

The impact of novel technologies on ablation therapy in scar-related tachycardia

Masateru Takigawa

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université BORDEAUX

| 3 | THÈSE F | PRÉSENTÉE |
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| 7 | L'UNIVERSITÉ | É DE BORDEAUX |
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| 9 | Science de la | Vie et de la Sant. |
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| 12 | Masateru Tak | igawa, MD, PhD |
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| 14 | L'impact des nouvelles techno | ologies sur la thérapie d'ablation |
| 15 | dans la tachycard | ie liée aux cicatrices |
| 16 | | |
| 17 10 | Sous la direction de | Professeur Pierre JAIS |
| 10 19 | | |
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| 22 | | |
| 23 | Membres du jury: | |
| 24 | | |
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| 31 | | |
| 32 | | |

| 33 | Declaration |
|----|--|
| 34 | |
| 35 | This dissertation is the result of my own work and includes nothing which is the outcome of work done in |
| 36 | collaboration except where specifically indicated in the text. It has not been submitted for any other degree or |
| 37 | qualification. |
| 38 | Much of my work from this thesis has been published or is in press, and the relevant citations are listed in the |
| 39 | following pages. |
| 40 | |

| 41 | Publications |
|----|---|
| 42 | |
| 43 | Original manuscript |
| 44 | 1) Takigawa M, Relan J, Kitamura T, Martin CA, Kim S, Martin R, Cheniti G, Vlachos K, Massoullié G, Frontera |
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- 131 Best Abstract Awards in APHRS 2018
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138 139

Titre : L'impact des nouvelles technologies de cartographie sur la thérapie d'ablation dans la tachycardie liée à la cicatrice

Résumé

140 Les innovations telle que les cathéters irrigués et le contact force ont largement amélioré la sécurité et l'efficacité de

141 l'ablation, et plusieurs technologies de ballon comme le cryoballon ont également raccourci le temps de procédure.

142 L'électroporation permettrait de réduire considérablement les complications tout en conservant la durabilité et la

143 transmuralité de la lésion. Cependant, de tels développements dans les techniques d'ablation mais aussi dans les

144 technologies de cartographie sont indispensables pour de meilleurs résultats du traitement de l'arythmie.

145 Un circuit de tachycardie atriale (TA) ou de tachycardie ventriculaire (TV) a normalement un isthme critique pour

146 maintenir la tachycardie. L'identification cet isthme ainsi que la formation d'une lésion durable peuvent être des

147 facteurs limitants dans l'efficacité du traitement par ablation de ces tachyarythmies.

148 En plus de certaines techniques d'ablation, plusieurs technologies de cartographie permettant de guider l'ablation

149 ont récemment vu le jour. L'amélioration considérable des cathéters de cartographie et des technologies d'imagerie

150 peut notamment avoir un impact sur le diagnostic du mécanisme de la tachycardie et sur l'identification de substrats

151 et de circuits de tachycardies, conduisant à une meilleure efficacité de l'ablation.

152 Les cathéters multipolaires de cartographie sont de plus en plus utilisés pour l'analyse du substrat. Cependant,

153 l'impact clinique de l'espacement inter-électrodes et de la taille des électrodes sur les électrogrammes locaux n'a pas
154 été systématiquement étudié. De plus, l'efficacité clinique de l'utilisation d'un système de cartographie à ultra haute

résolution / haute densité et de cathéters multipolaires et à espace inter-électrodes réduits n'a pas été complètement
analysé.

157 Les données issues de l'imagerie cardiaque par résonnance magnétique (IRM) et de la tomodensitométrie (par

158 exemple zone de cicatrice, épaisseur de paroi) peuvent être combinées avec les informations électroanatomiques du

159 système de cartographie tridimensionnelle par un nouveau procédé de calcul 'MUSIC'. Toutefois, le véritable

160 impact clinique de cette technologie n'a pas été étudié.

161 Par conséquent, les objectifs de ce projet de recherche sont (1) de préciser en quoi les signaux sont affectés par la

162 différence de taille d'électrode et d'espacement inter-électrodes, et de démontrer les caractéristiques de chaque

163 cathéter multipolaire dans un modèle animal (2) afin de pouvoir observer le bénéfice clinique de l'utilisation d'un

164 système de cartographie ultra haute résolution / haute densité et des cathéters multipolaires à mini électrodes

165 espacées pour identifier une stratégie pratique permettant de détecter l'isthme du circuit de tachycardie et de le

166 traiter à l'aide de ces technologies, (3) d'évaluer le rapport entre les données d'imagerie et de voltage pour chaque

167 cathéter multipolaire, et (4) d'élucider l'impact clinique de l'ablation d'une TV guidée par l'imagerie avec le
168 système MUSIC.

100 Systeme WOSIC.

169 Pour élucider ces points, nous avons mené trois études principales comprenant une série d'expérimentations sur des

animaux et deux séries d'études cliniques. La première série de 4 expériences sur animaux a démontré l'effet de la

171 taille des électrodes, de l'espacement inter-électrodes, de l'orientation de l'activation des électrogrammes locaux et

172 du seuil de voltage déterminant les zones de cicatrices.

- 173 La partie clinique est composée de deux études principales. Premièrement, nous avons élucidé l'efficacité de
- 174 l'utilisation du nouveau système de cartographie à ultra haute résolution / haute densité, «RhtymiaTM», associé au
- 175 cathéter multipolaire OrionTM muni de mini électrodes et d'un espacement inter-électrodes, dans le diagnostic de
- 176 plusieurs formes de TA complexes post-FA. La deuxième partie de l'étude clinique décrit la relation entre la
- 177 distribution de l'épaisseur de paroi en tomodensitométrie et la cartographie du substrat par système de cartographie
- 178 électroanatomique chez les patients avec tachycardie ventriculaire sur cardiomyopathie ischémique. Nous
- 179 démontrons également une efficacité clinique des données de l'imagerie sur la cartographie de l'isthme des
- 180 tachycardies ventriculaires.
- 181 Ma série d'études donne ainsi un aperçu des avantages et des limites des technologies de cartographies récentes
- 182 (système de cartographie haute résolution / haute densité avec cathéters multipolaires et tomodensitométrie), tant du
 183 côté expérimental que clinique.
- 184

185 Mots clés: Tachycardie auriculaire, tachycardie ventriculaire, cicatrice, imagerie, 186 cartographie

| 187 | Title: The impact of novel mapping technologies on ablation therapy |
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| 188 | in scar-related tachycardia |
| 189 | |
| 190 | |
| 191 | Summary |
| 192 | |
| 193 | Recent improvement in ablation such as irrigation catheter and contact force has been dramatically raised a safety |
| 194 | and efficacy, and several balloon technologies such as cryoballoon has significantly shorten the procedure time. |
| 195 | Electroporation may remarkably decrease complications with maintaining a lesion durability and transmurality. |
| 196 | However, not only such developments in ablation technologies but also those in mapping technologies are |
| 197 | mandatory for the best outcome of an arrhythmia treatment. |
| 198 | A circuit of atrial tachycardia (AT) and ventricular tachycardia (VT) normally has a critical isthmus to maintain the |
| 199 | tachycardia. Successful detection of this isthmus as well as a durable lesion formation can be a limiting factor in the |
| 200 | efficacy of ablation therapy for these tachyarrhythmias. |
| 201 | In addition to some ablation technologies, several mapping technologies for guiding ablation therapy have recently |
| 202 | emerged. In particular, the remarkable improvement of mapping catheters and imaging technologies may have an |
| 203 | impact on diagnosing a tachycardia mechanism and identifying substrates and circuits of tachycardias, leading to a |
| 204 | procedural efficacy. |
| 205 | Multipolar mapping catheters are increasingly utilized for substrate delineation. However, the clinical impact of |
| 206 | inter-electrode spacing and size of the electrode on the local electrograms has not been systematically examined. |
| 207 | Additionally, the clinical efficacy of using an ultra high resolution/high-density mapping system and multipolar |
| 208 | catheters with small electrodes and spacing has not been fully examined. |
| 209 | Imaging information from Cardia Magnetic Resonance (CMR) and computerized tomography (CT) scan (e.g. scar |
| 210 | area, wall thickness) can be combined with the electroanatomical information from the 3 dimensional mapping |
| 211 | system by a novel computational tool 'MUSIC' system. However, the true clinical impact of this technology has |
| 212 | not been reported. |
| 213 | Therefore, the aims of this research project are to (1) clarify how the signals are affected by the difference of |
| 214 | electrode length and interelectrode spacing, and demonstrate the characteristics of each multipolar catheter in an |
| 215 | animal model (2) to observe a clinical advantage of using an ultra high resolution/high-density mapping system and |
| 216 | multipolar catheters with small electrodes and spacing in identifying a practical strategy to detect the isthmus of the |
| 217 | tachycardia circuit and treat it based on these technologies, (3) to evaluate the relation between the information |
| 218 | from imaging and voltages in each multipolar catheter, and (4) to elucidate the clinical impact of an imaging |
| 219 | guided-VT ablation therapy with the MUSIC system. |
| 220 | To elucidate these points, we conducted three main studies including one series of animal experiments and two series |
| 221 | of clinical studies. The first series of 4 animal experiments demonstrated the effect of electrode size, inter-electrode |
| 222 | spacing, and activation orientation on the local electrograms and voltage threshold determining scars. |
| 223 | The clinical parts composed of two main studies. First, we elucidated the efficacy of using the novel ultra high- |
| 224 | resolution/high-density mapping system, 'Rhtymia TM ', with the Orion TM multipolar catheter with small electrodes and |

- inter-elecotrode spacing catheter, in diagnosing several forms of complex post-AF ATs. The second part of the clinical
- study describes the relationship between wall thickness distribution on CT imaging and substrate mapping on the
- 227 electroanatomical mapping system in patients with ventricular tachycardias based on ischemic cardiomyopathy. We
- also demonstrates a clinical efficacy of imaging information on mapping the isthmus of ventricular tachycardias.
- 229 My study series thus provide an insight into the advantage and limitation of recent mapping technologies (high-
- resolution/high-density mapping system with multipolar catheters and CT imaging) from both experimental and clinical sides.
- 232

233 Keywords: Atrial tachycardia, ventricular tachycardia, scar, imaging, mapping

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275 Abbreviations

- 276
- 277 AAD, anti-arrhythmic drug
- AF, atrial fibrillation
- AFL, atrial flutter
- 280 AMAT, anatomical macroreentrant AT
- AT, atrial tachycardia
- 282 AUROC, area under the ROC curve
- 283 BiAT, biatrial tachycardia
- 284 CA, catheter ablation
- 285 CMR, cardiac magnetic resonance
- 286 CS, coronary sinus
- 287 CT, computed tomography
- 288 CTI, cavotricuspid isthmus
- 289 DAD, delayed afterdepolarization
- 290 DE-MRI, delayed enhanced magnetic resonance imaging
- EAD, early afterdepolarization
- 292 EAM, electroanatomical mapping
- EGM, electrogram
- 294 ICD, implantable cardioverter defibrillator
- 295 ICM, ischemic cardiomyopathy
- LA, left atrium
- 297 LAA, left atrial appendage
- 298 LAVA, local abnormal ventricular activity
- 299 LP, late potential
- 300 LV, left ventricle
- 301 MA, mitral annulus
- 302 MAT, macroreentrant AT
- 303 MB, Marshall bundle
- 304 MDCT, multiple detector computed tomography
- 305 MI, mitral isthmus
- 306 NICM, non-ischemic cardiomyopathy
- 307 PMF, perimitral flutter
- 308 PPI, post pacing interval
- 309 PTF, peritricuspid flutter
- 310 PV, pulmonary vein
- 311 PVC, premature ventricular contraction
- 312 RAT, reentrant atrial tachycardia

- 313 RF, radiofrequency
- 314 RFA, radiofrequency ablation
- 315 RMAT, roof-dependent macroreentrant AT
- RV, right ventricle
- 317 SCD, sudden cardiac death
- 318 SMVT, sustained monomorphic ventricular tachycardia
- 319 SVT, supraventricular tachycardias
- 320 TA, tricuspid annulus
- 321 TCL, total cycle length
- 322 VOM, vein of Marshall
- 323 VF, ventricular fibrillation
- 324 VT, ventricular tachycardia
- 325 WT, wall thickness

| 327 | CONTENTS | | |
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3. INTRODUCTION

430 **3-1. Background**

Conventional radiofrequency (RF) ablation has revolutionized the treatment of many supraventricular tachycardias
(SVTs) as well as ventricular tachycardias (VTs). Successful stabilization of arrhythmias with predictable anatomical
locations or characteristics identified on endocardial electrograms, such as idiopathic VT, atrioventricular nodal
reentrant tachycardia (AVNRT), or typical atrial flutter (AFL), has approached rates of 90% to 99%.

Since Michel Haissaguerre (cardiac electrophysiologist in Bordeaux, France) first reported pulmonary veins (PVs)
as a main source of atrial fibrillation (AF) in 1998¹ and demonstrated in human hearts that AF sources in PVs can be
removed by ablation, electrical PV isolation (PVI) has become a first-line management strategy for AF². Although
PVI for paroxysmal AF has become a standard treatment, the strategy for persistent AF has not been established.

Several strategies including linear ablation^{3–5}, CFAE ablation⁶, EGM-based ablation⁷, driver ablation⁸, and others have been attempted. Although some of these have demonstrated excellent results, a randomized trial did not show the superiority of additional extensive ablation with PVI⁹. Conversely, these extensive approaches may lead to more complex tachyarrhythmias. Additionally, because of the great advancement in cardiac surgery for congenital heart disease, many adult patients can now undergo procedures to correct complex atrial tachycardia (AT). However, regarding atrial arrhythmias, the ablation of complex scar-related AT continues to pose a major challenge.

445 Regarding ventricular arrhythmias, over the past two decades, VT ablation for patients with ischemic (ICM) and non-446 ischemic cardiomyopathy (NICM) has emerged as a successful adjunctive therapy to implantable cardioverter 447 defibrillators (ICD) and anti-arrhythmic drug (AAD) therapy. Although ICDs are effective for terminating VT and ventricular fibrillation (VF), repetitive shocks significantly impair quality of life¹⁰⁻¹², and inappropriate ICD shocks 448 in patients with heart failure are associated with increased mortality¹³. AADs have an important role in shock 449 450 reduction; however, these agents often have limited efficacy and significant side effects^{14,15}. VT ablation is an 451 important therapeutic intervention in cases of recurrent VT when drugs are either ineffective or poorly tolerated. In 452 terms of strategy, VT ablation was based primarily on activation and entrainment mapping, with the end point being 453 non-inducibility of VT¹⁶. Entrainment mapping during VT can be performed to electrophysiologically confirm 454 critical isthmuses or exit sites to determine if ablation should be performed. However, because most VTs are poorly 455 tolerated hemodynamically, and because induced VTs are not always clinically relevant, an approach involving 456 substrate mapping is more commonly used to guide ablation. One of the first studies to demonstrate the potential 457 efficacy of targeting substrates was performed by De Bakker et al, who described scar-related VT circuits related to surviving bundles associated with a zig-zag course resulting in slow conduction (Figure 3-1)^{17,18}. Subsequently, it 458 459 was reported that the substrate that was initially described for myocardial infarction is similarly responsible for scar 460 related re-entrant VTs that occur with other cardiac disease. However, detection of arrhythmogenic substrates in 461 patients with scar-related VTs is challenging. A dramatic advancement in recent mapping technology may assist with 462 the identification of an arrhythmogenic substrate in these scar-related tachycardias in the atrium and the ventricle.

- 463
- 464
- 465

Left





467 Figure 3-1. Zig-zag conduction in the infarct region^{17,18} 468 Left side: A section of the endocardial wall of a resected posterior papillary muscle that was located close to the site of origin of a ventricular tachycardia. 469 The section was taken perpendicular to the fiber direction. The papillary muscle was investigated in a super-fused tissue bath. The central part of the 470 muscle was composed of dense connective tissue (marked by C on the left). A rim of surviving muscle fibers (marked by R) surrounded the core of 471 fibrous tissue. Myocytes were grouped together, separated by strands of fibrous tissue. The number of myocytes within a cluster varied markedly along 472 lines perpendicular to the fiber direction. Midle, A schematic drawing of the section. Dotted areas indicate viable muscle bundles; black areas point to 473 connective tissue. Tracings on the right are extracellular recordings (signals are traced from oscilloscope pictures) made at 0.2mm distances from sites A 474 to M during stimulation at a site 3mm from A toward the base of the papillary muscle. A reference signal (the upper tracing marked Ref) was recorded 475 6.5mm from site M toward the tip. Recordings show a varying degree of fractionation, depending on the number of bundles near the recording site. 476 Right side: Schematic representation of the slowly conducted electrical propagation with inside the scar. Black trace shows the tortuous route that 477 activation might have followed perpendicular to the fiber direction from the left side of tract A to the right side of tract B. The length of the route from 478 the left side of tract A to the left side of tract B was 25.2mm, which is 18 times longer than the shortest distance between the tracts A and B (1.4mm). 479

480 **3-2. Mechanisms of tachycardia**

481 There are three main mechanisms of tachycardia: abnormal automaticity, triggered activity, and macro-reentry¹⁹.

482 Automaticity

483 Atrial and ventricular myocardial cells do not display spontaneous diastolic depolarization or automaticity under 484 normal conditions, but they can develop these characteristics when depolarized, resulting in the development of 485 repetitive impulse initiation, a phenomenon termed depolarization-induced automaticity. The membrane potential at 486 which abnormal automaticity develops ranges between -70 and -30 mV. The rate of abnormal automaticity is 487 substantially higher than that of normal automaticity and is a sensitive function of resting membrane potential (i.e., 488 the more depolarized resting potential, the faster the rate).

489 *Triggered activity*

490 Depolarizations that occur with or follow the cardiac action potential and depend on preceding transmembrane 491 activity for their manifestation are referred to as afterdepolarizations. Two subclasses are traditionally recognized:

492 early and delayed. Early afterdepolarization (EAD) interrupts or restricts repolarization during phase 2 and/or phase

493 3 of the cardiac action potential, whereas delayed afterdepolarization (DAD) occurs after full repolarization. When

494 EAD or DAD amplitude are sufficient to achieve the threshold potential of the membrane, spontaneous action

- 495 potential referred to as a triggered response results. These triggered events lead to extrasystoles, which can precipitate
- 496 tachyarrhythmias.

497 *Reentry*

498Reentry is fundamentally different from automaticity or triggered activity depending on the mechanism by which it499initiates and sustains cardiac arrhythmias. Circus movement reentry occurs when an activation wavefront propagates

around an anatomic or functional obstacle or core and re-excites the site of origin (**Figure 3-2**)²⁰. During this type of

501 reentry, all cells take turns in recovering from excitation so that they are ready to be excited again when the next

502 wavefront arrives. In contrast, reflection and phase 2 reentry occur in a setting in which large differences of recovery

503 from refractoriness exist between sites. The site with delayed recovery serves as a virtual electrode that excites its

already recovered neighbor, resulting in reentrant re-excitation. In addition, reentry can be classified as anatomic and

505 functional, although there is a gray zone in which both functional and anatomic factors are important for determining

506 the characteristics of reentrant excitation.



508 Figure 3-2. Ring models of reentry.

509 (A) Schematic of a ring model of reentry. (B) Mechanism of reentry in the Wolf-Parkinson-White syndrome involving the AV node and an 510 atrioventricular accessory pathway (AP). (C) A mechanism for reentry in a Purkinje-muscle loop proposed by Schmitt and Erlanger. The diagram 511 shows a Purkinje bundle (D) that divides into 2 branches, both connected distally to ventricular muscle. Circus movement was considered possible if 512 the stippled segment, A / B, showed unidirectional block. An impulse advancing from D would be blocked at A, but would reach and stimulate the 513 ventricular muscle at C by way of the other terminal branch. The wavefront would then reenter the Purkinje system at B traversing the depressed region 514 slowly so as to arrive at A following expiration of refractoriness. (D) Schematic representation of circus movement reentry in a linear bundle of tissue 515 as proposed by Schmitt and Erlanger. The upper pathway contains a depressed zone (shaded) that serves as a site of unidirectional block and slow 516 conduction. Anterograde conduction of the impulse is blocked in the upper pathway but succeeds along the lower pathway. Once beyond the zone of 517 depression, the impulse crosses over through lateral connections and reenters through the upper pathway. (C and D from Schmitt FO, Erlanger J. 518 Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillary contractions²¹.)

520 The following criteria developed by Mines^{22,23} for the identification of circus movement reentry remain in use today: 521 an area of unidirectional block must exist; the excitatory wave progresses along a distinct pathway, returning to its

- 522 point of origin and then following the same path again; and interruption of the reentrant circuit at any point along its
- 523 path should terminate the circus movement.
- 524 It was recognized that successful reentry could occur only when the impulse was sufficiently delayed in an alternate 525 pathway to allow for expiration of the refractory period in the tissue proximal to the site of unidirectional block. Both 526 conduction velocity and refractoriness determine the success or failure of reentry, and the general rule is that the 527 length of the circuit (path length) must exceed or equal that of the wavelength, with the wavelength defined as the 528 product of the conduction velocity and the refractory period or that part of the path length occupied by the impulse 529 and refractory to re-excitation. Therefore, the theoretical minimum path length required for development of reentry 530 was dependent on both the conduction velocity and the refractory period. Reduction of conduction velocity or APD 531 can significantly reduce the theoretical limit of the path length required for the development or maintenance of reentry.
- 532

533 **3-3. Mechanism of scar-related tachycardia**

- With scar-related tachycardias, the main mechanism is reentry. Within the scar, bundles of surviving myocytes with damaged intracellular connections (Connexin 43), electrically inactive regions, fibrosis (elastin and collagen), calcification, and fat can be found. These conditions are known to be associated with increased anisotropy, slow conduction, and block critical to the reentry circuit.
- 538 In scar-related AT, these scars may originate from atrial scarring after prior heart surgery or ablation, but they could 539 also occur in any form of heart disease or be idiopathic^{24–26}. However, an increasing number of complex scar-related 540 AT may be due to extensive ablation for persistent AF^{27-29} .
- 541 With scar-related VT, the majority of ventricular scars are related to fibrosis after ventricular inflammation or 542 ischemia. With NICM, scars distribute in a patchy manner, more extensively, and predominantly intramural to the 543 epicardial LV wall. In contrast, in ICM, scars due to myocardial ischemia present as wave-like necrosis starting from 544 the endocardium and progressing toward the epicardium³⁰.
- 545

546 **3-4. Treatment of scar-related tachycardias (ATs and VTs)**

- 547 Treatment of scar-related AT is based on rate control and rhythm control. For rate control, beta-blockers, diltiazem, 548 or verapamil are recommended, and anticoagulation may be considered for patients at risk for thrombosis. However, 549 it may be difficult to achieve rate control in patients with scar-related AT, especially in post-AF ablation non-CTI-550 dependent flutter. When the ventricular response cannot be controlled with common rate-control medications, 551 restoration of the sinus rhythm should be considered. Although pharmacological therapy including amiodarone, 552 dofetilide, sotaloland, or class I antiarrhythmics (for patients without any structural heart disease) can be used, 553 catheter ablation (CA) is the first-line therapy. The superiority of CA over AAD for recurrent AT after persistent AF 554 ablation with regard to SR maintenance, long-term safety, and improvements in quality of life has been reported³¹. 555 In contrast to scar-related AT, scar-related VT, which is often sustained monomorphic VT (SMVT), is life-threatening
- arrhythmia associated with sudden cardiac death. Chronic therapy of patients with SMVT usually requires utilization

- 557 of multiple therapeutic modalities, including ICD, AADs, CA, and/or arrhythmia surgery.
- 558 ICD therapy: Patients who survive an episode of SMVT in the setting of structural heart disease (post-MI or
- nonischemic cardiomyopathy) are typically candidates for implantation of an ICD to treat recurrent VT and reduce
- the risk of SCD^{32–37}. Although some patients are treated with other therapies such as AADs, RF ablation, or surgery,
- an ICD is the most common initial treatment for SMVT; however, survival benefits and superiority of the ICD over
- other therapies have not been established for any particular therapy because these patients were excluded from ICD
- trials. These other therapies are used either as an adjunct to an ICD or as an alternative for patients who are not
- candidates for or who refuse ICD therapy.
- *Antiarrhythmics:* Beta-blocker therapy is indicated for nearly all patients who experience VT, including patients with prior MI, heart failure, reduced LV systolic function, and others. Beta-blockers provide some level of protection against recurrent VT. No other antiarrhythmic medication has been demonstrated to reduce the mortality rates of patients with sustained monomorphic VT. Therefore, the use of AADs for patients should be limited to two settings: as an adjunct to an ICD for patients with frequent arrhythmia recurrences and ICD shocks and as primary therapy or an adjunctive therapy to CA for patients who do not want or who are not candidates for an ICD. Amiodarone and sotalol may be used in this case.
- 572 *Catheter ablation:* For patients with recurrent SMVT resulting in ICD shocks despite treatment with an AAD, we 573 suggest catheter-based RFA rather than the addition of a second antiarrhythmic agent³⁸. RFA is also an alternative to 574 AADs as the initial therapy for SMVT patients who do not desire AADs. Prophylactic substrate-based catheter 575 ablation reduced the incidence of ICD therapy for patients with a history of myocardial infarction who received an 576 ICD for the secondary prevention of sudden death³⁹. It would be an option for the management of ventricular 577 arrhythmias in patients with advanced heart failure⁴⁰. In addition, RFA, with or without AAD therapy, is an option 578 for patients with SMVT who are not candidates for or who refuse ICD implantation.
- 579

580 **3-5. Mapping of scar-related tachycardia**

581 Cardiac mapping refers to the process of identifying the temporal and spatial distributions of myocardial electrical 582 potential during a particular heart rhythm. Cardiac mapping is a broad term that covers several modes of mapping, 583 such as body surface, endocardial, and epicardial mapping. Cardiac mapping during tachycardia aims at elucidating 584 the mechanism(s) of tachycardia, describing the propagation of activation from its initiation to its completion within 585 a region of interest, and identifying the site of origin or a critical site of conduction to serve as a target for catheter 586 ablation. Several methods of electrophysiologically mapping tachycardias have been reported, such as entrainment 587 mapping, activation mapping, pace mapping, and substrate mapping. Because mapping during the tachycardia should 588 be a fundamental approach, entrainment mapping and activation mapping are frequently used for both ATs and VTs. 589 For scar-related AT, the AT circuit and the critical isthmus are usually identified during tachycardia based on 590 entrainment mapping and activation mapping $^{41-43}$. However, in contrast to scar-related AT, the majority of patients 591 with VTs and structural heart disease presenting for CA have hemodynamically unstable VTs that prevent accurate 592 delineation of the the reentrant circuit and its critical isthmus with activation mapping or entrainment mapping. 593 Therefore, pace mapping and substrate mapping are used to characterize areas likely to support reentry based on 594 electrophysiological characteristics that can be determined during stable sinus or paced rhythm. Mapping allows for

- 595 the elimination of VT, irrespective of inducibility or hemodynamic tolerance. Even for hemodynamically stable VTs,
- substrate mapping is often used to limit activation mapping or entrainment mapping, and to target a region of interest.
- 597 Current criteria used to define the abnormal arrhythmogenic substrate rely on a combination of lower bipolar or
- 598 unipolar voltage and abnormal electrogram characteristics (e.g., fragmented, split, and late electrograms). These
- 599 abnormal electrogram features can represent slow or delayed activation that comprises surrogate markers for potential
- 600 VT circuits.
- 601

602 **3-5-A. Entrainment mapping**

- 603 Entrainment mapping is an established electrophysiological technique used to identify arrhythmia mechanisms and 604 define components of the reentrant circuit. First described in the late 1970s by Waldo et al⁴¹, entrainment mapping was subsequently used to localize areas of the myocardium that were within a reentrant circuit during both atrial 605 macroreentry⁴²⁻⁴⁴ and ventricular tachycardia⁴⁵. Macroreentry was diagnosed when at least two atrial pacing sites at 606 least 2 cm apart were within the circuit (post-pacing interval (PPI) minus total cycle length (TCL) [PPI-TCL], 20 607 608 ms)⁴⁶ and/or when orthodromic capture of upstream electrograms from a downstream pacing site could be demonstrated⁴⁷. Sites were considered within the circuit if the PPI-TCL was 20 ms. Sites with PPI-TCL between 20 609 610 and 40 ms were considered intermediate. Sites with PPI-TCL of 40 ms were thought to be outside the active circuit. 611 In scar-related VT with entrainment mapping, good ablation sites have identical stimulus to QRS (S-QRS) and EGM-QRS time, short PPI-TCL (<30 ms), and concealed entrainment.⁴⁵ The relation between a given local site and the VT 612
- 613 circuit can be mapped using entrainment mapping as shown in the **Figure 3-5**.



614

615 Figure 3-5-1. Practical use of entrainment mapping

616 Left side: Flow diagram for classification of mapping sites in a model of scar-related ventricular tachycardia. The bottom shows a schematic model of a 617 double loop re-entry circuit with multiple bystander sites. Pacing from sites indicated by black arrows are likely to exhibit concealed fusion, while areas

- 618 outside the re-entry circuit (grey arrows) would likely show QRS fusion (see text for discussion). Right side: Entrain- ment of ventricular tachycardia 619 with a cycle length (TCL) of 400 milliseconds with findings that would be consistent with pacing at the two re-entry circuit sites indicated. From the top 620 are surface ECG leads I, II, III, V1, and V5 and intracardiac recordings from the mapping catheter (abl) and distal His bundle catheter. (A) Pacing from 621 the distal ablation catheter with a CL of 370 milliseconds reveals entrainment with concealed fusion; stimulus-to-QRS interval (100 milliseconds) minus 622 electrogram-to-QRS interval (60 milliseconds) = 40 milliseconds and a PPI of 430 milliseconds, both indicating that the pacing site is likely in an adjacent 623 bystander region close to the isthmus (PPI - TCL = 30 milliseconds). The local electro- gram is low-voltage. (B) Pacing at an adjacent site (lower right 624 panel) shows concealed fusion and a PPI equal to TCL, indicating an isthmus site. The local electrogram recorded at the disal ablation catheter (ABL d) 625 from this site is broader and appears highly fractionated. The stimulus-to- QRS interval of 100 milliseconds is consistent with a location near the exit, 626 and is only 10 milliseconds longer than the electrogram-to-QRS interval (90 milliseconds). S-QRS = stimulus-to-QRS interval.
- 627

628 **3-5-B. Activation mapping**



629

630 Figure 3-5-2. Activation patterns in tachycardias

631

Activation mapping is another important method of identifying the optimal ablation site for AT. Because scar-related AT frequently shows the reentrant mechanism, intracardiac activity should be present at some point in the heart throughout the cardiac cycle. For mapping reentrant tachycardias, the goal of mapping is identification of the critical isthmus of the reentrant circuit including macroreentrant ATs (MATs). EGMs are typically recorded through at least 70-90% of the TCL in reentrant AT. Reentrant AT is typically characterized by earlier EGM timing in diastole; furthermore, mid-diastole (or even earlier) potential has been correlated with successful ablation sites.

638 In scar-related VT, both activation mapping and entrainment mapping are powerful tools that can identify the VT 639 circuit and critical isthmus. Ideally, the entire VT cycle length can be mapped by contact mapping with a bipolar catheter or a multipolar catheter⁴⁸. In scar-related VT, a zone of slow conduction over a pathway of possibly complex 640 641 geometry (e.g., nonlinear, nonhomogenously anisotropic) provides the diastolic limb of the reentrant circuit. After 642 emerging from the zone of slow conduction, the wavefront propagates rapidly throughout the ventricles to generate 643 the QRS complex. Therefore, mid-diastolic potential, which indicates an isolated area of the isthmus bordered by an 644 anatomical obstacle and/or dense scar without excitable tissue, and early or presystolic potential, which indicates the 645 close proximity to the exit region from the zone of slow conduction, should be targeted as ablation sites.

647 **3-5-C. Pace mapping**

648 Pace mapping is a technique designed to help locate tachycardia sources by pacing at different endocardial sites to 649 reproduce the ECG morphology of the tachycardia. Pace mapping is based on the principle that pacing from the site 650 of origin of a focal tachycardia at a pacing CL similar to the tachycardia CL will result in the same activation sequence 651 as that during the tachycardia. With this technique, the origin of a PVC or VT can be localized by stimulating the 652 myocardium to reproduce clinical 12-lead morphology when it is difficult to induce clinical VT or when the VT is 653 hemodynamically unstable. The optimal site should exactly match the tachycardia QRS, including individual notches 654 and major deflections. The results of a comparison of the 12-lead ECG during pace mapping and VT are usually 655 expressed using a scale from 0 to 12. Manufacturer-specific algorithms (Labsystem Pro, Boston Scientific, Arden 656 Hills, MN [formerly Bard]; PaSo CARTO module, Biosense Webster, Diamond Bar, CA; Rhythmia, Boston 657 Scientific, Marlborough, MA; and EnSite Precision, Abbott Laboratories, Abbott Park, IL) provide templatematching algorithms to quantify the difference between VT morphology and pace maps^{49,50}. Multiple scar exit sites 658 659 (MES; all with $\geq 10/12$ match with VT) from the scar can be seen when performing pace mapping (10 mA, 2 ms) at 660 an abnormal EGM site presenting with ≥ 2 pace-map morphologies (<10/12 match) at the same pace-map drive train 661 (400-600 ms). A recently developed technique uses high-density pace mapping for the visualization of the critical isthmus (orientation and length). With this technique, a detailed color-coded pace map is created. Although exit sites 662 663 characteristically have perfect pace maps, entrance sites have the worst pace maps but show abrupt changes in pace-664 map matches, which indicate the location of the isthmus. The S-QRS interval is also an important 665 parameter. Ventricular pacing in normal myocardium is associated with an S-QRS interval less than 40 ms. However, 666 an S-QRS interval more than 40 ms is consistent with slow conduction from the pacing site and is typically associated 667 with abnormal fractionated EGMs recorded from that site. Therefore, pace mapping can provide a measure of slow conduction, as indicated by the S-QRS interval^{51,52}. Parts of the VT reentry circuit isthmuses can be traced during 668 669 NSR by combining both the QRS morphology and the S-QRS delay from pace mapping in anatomical maps.

Importantly, the pacing rate has been reported to alter the QRS morphology; therefore, a pacing rate close to the VT rate should be used⁵³. Pacing at stimulus strengths only slightly greater than the threshold is desirable to avoid capture over a large area, which can reduce accuracy; however, checking the threshold at each mapping point is timeconsuming and might not be practical.

674

675 **3-5-D. Substrate mapping**

676 Voltage criteria for scar identification

677 Scar tissue can be identified based on the bipolar electrogram amplitude. A value of <0.5 mV indicates a dense scar; 678 this value was previously determined through intraoperative mapping using an ablation catheter for patients with post-infarction VT⁵⁴. Additionally, a value of >1.5 mV indicates healthy tissue; this value is based on voltage mapping 679 680 of the normal heart in the absence of structural disease⁵⁵. Voltage between 0.5 mV and 1.5 mV defines abnormal low-681 voltage areas⁵⁶. For epicardial mapping, a low-voltage threshold <1 mV is used for abnormal late, split, and wide potential >80 ms^{54,57,58}. Unipolar low-voltage thresholds to identify scars are -<5.5 mV in the RV and <8.3 mV in the 682 683 LV. Unipolar voltages provide information over a wider field; therefore, they are valuable for predicting the presence of intramural or epicardial scars^{59,60}. 684

685 *Other electrogram characteristics as ablation targets*

Low-voltage areas in scars are often large, and not all are related to VT. To avoid unnecessarily extensive ablation, 686 687 several other EGM features acquired during sinus rhythm or elicited by pacing maneuvers have been studied to 688 identify areas potentially related to VT within the scar. In the seminal study by de Bakker et al¹⁷, the authors 689 demonstrated the presence of heterogeneous "zig-zag" conduction within the infarcted area, which was related to the 690 presence of poor cell-to-cell coupling of surviving myocyte bundles interspersed among fibrous tissue. In these 691 regions, abnormal fractioned and LPs were recorded. Clinical studies have adopted heterogeneous definitions of 692 abnormal electrograms with nonuniform use of terms such as "fragmented," "split," and "late"; however, the 693 relationship between these surrogate markers and VT circuits remains to be thoroughly explored⁶¹. Therefore, local 694 abnormal ventricular activities (LAVAs) may include all abnormal ventricular signals representing nearfield signals 695 from poorly coupled fibers within scars indicating potential VT isthmus sites⁶².

696

697 **3-6. Tools for cardiac mapping**

698 **3-6-A. Electroanatomical Mapping Systems**

699 Cardiac electrical information obtained from catheter-mounted electrodes and 3D spatial location information can be 700 combined by an electroanatomical mapping (EAM) system to reconstruct an image that represents the targeted 701 cardiac chamber⁶³. Several 3D EAM systems are commonly used in clinical practice, as shown in the **Figure 3-6-1**.



702

703 Figure 3-6-1. Three major mapping systems used in the industry

704

705 The EnSite Precision system (Abbott Laboratories, Abbott Park, IL; formerly EnSite Velocity and EnSite NavX, St. 706 Jude Medical, St. Paul, MN) localizes diagnostic and ablation catheters based on the voltage and impedance 707 measurements. With the use of proprietary catheters, the EnSite Precision system can now add magnetic-based

- information to the map that can aid accurate localization.
- 709 The CARTO mapping system (current version of CARTO 3; Biosense-Webster, Diamond Bar, CA) can accurately
- 710 display the localization of proprietary mapping and ablation catheters based on magnetic field differences. Using this

system, the electrodes and shafts of various diagnostic catheters are visualized based on the impedance-based

- algorithm. A proprietary intracardiac ultrasound catheter can interface with the mapping system to further define
- cardiac geometry within the mapping field⁶⁴.
- The Rhythmia HDx mapping system (Boston Scientific, Marlborough, MA) uses both magnetic-based and
- impedance-based methods for catheter tracking. A prominent feature of this system is the proprietary 64-pole mini-
- 716 basket catheter with closely spaced electrodes.
- 717

The principles of cardiac electrophysiology are essential to create maps that accurately represent physiology and anatomy. Although it is generally accepted that the use of the EAM system can reduce fluoroscopy time and allow for more precise mapping, it is also important to understand that maps created using EAM systems are considerably affected by various factors such as annotation of EGM qualities, catheter-tissue contact, distribution and density of sampled points in the map, the rhythm being mapped, direction and velocity of the activation wavefront, and the size

- and spacing of the electrodes.
- Numerous technologies have been developed or are in development to improve mapping quality and user experience.
- These include automated chamber segmentation, imported scar delineation from alternative cardiac imaging such as cardiac magnetic resonance (CMR), computed tomography (CT), and echocardiography, and automated electrogram analysis tools. Ultra-high-density mapping catheters have significantly changed the resolution of scar features and, as a result, our understanding of tachycardia circuit physiology.
- EAM has been proven to be a versatile technology for guiding treatment of a wide range of arrhythmias. EAM provides an impact by offering the operator the possibility of using various mapping strategies, including activation maps, entrainment maps, pace maps, electrogram amplitude (voltage) maps, propagation maps, Isochronal maps, and tagging location of specific electrograms of interest.
- 733

734 **3-6-B.** Multipolar Mapping Catheters

Although the development of 3D-EMS had a huge impact on the field of ablation treatment, it has several limitations. To acquire electroanatomical information, the ablation catheter has to have constant contact with the heart. With an ablation catheter, which usually comprises a 4-mm-tip electrode and a 2-mm-ring electrode separated by 1 mm of spacing⁵⁵, this mapping process requires extensive time, and the geometry between two points is a black box; therefore, the created geometry is not precise because of a low density of points, as shown in the Figure 3-6-2⁵⁵.

Voltage map reported in 2000 4mm-tip ablation catheter



[•] Circulation. 2000;101:1288-1296

741 Figure 3-6-2. Conventional point-by-point mapping with an ablation catheter

742

740

743 With the introduction of mapping systems capable of acquiring data simultaneously from multiple sites for each beat, 744 an increasing number of multielectrode mapping catheters has been used over the past several years as shown in the 745 Figure 3-6-3. These catheters provide several advantages, particularly regarding mapping density, resolution, and 746 speed. The ability to record EGMs from multiple sites at each beat not only increases the number of points but also 747 decreases the mapping time. Smaller electrodes with shorter interelectrode spacing are frequently used for these 748 multipolar catheters, resulting in increasing mapping density and resolution, which may be better for the identification 749 of surviving myocardial bundles within heterogeneous scar tissue that may be missed with standard ablation catheters with larger electrodes and spacing $^{65-69}$. These catheters may also be useful for activation mapping during tachycardia 750 751 due to rapid acquisition of multiple points from several sites with high spatial resolution, which can facilitate the 752 identification of a reentry isthmus or origin of tachycardia⁶⁹.

Currently, several multielectrode catheters are available. The Pentaray catheter (Biosense Webster, Diamond Bar, CA) is shaped like a flower and has five splines, each with four electrodes (a total of 20 electrodes), which can be used with the CARTO EAM system. Each electrode is 1 mm in size, and inter-electrode spacing between the bipole is 2 mm (center to center). This catheter frequently causes ectopic beats in areas of contracting myocardium, and spatial sampling is nonuniform due to the variable spread of the splines and limited contact with the myocardium.

- 758 The Advisor HD Grid catheter (Abbott Laboratories, Abbott Park, IL) is shaped like a flat broom with a novel four-
- by-four unipolar electrode array that can be used in conjunction with the EnSite Precision system⁷⁰. Each electrode
- is 1 mm in size and equidistantly spaced 4 mm (center to center) apart from each other. A potential advantage is the
- uniform spatial sampling; however, the collection of ventricular mapping data in humans in vivo is currently notpossible.

The third catheter is a small basket catheter with 64 very small electrodes arranged on eight splines that can be used with the Rhythmia EAM system (Orion; Boston Scientific, Marlborough, MA)^{69,71}. Each electrode is 0.4 cm² in size, and the inter-electrode spacing is 2.5 mm. Specifically, the unidirectional and extremely small printed electrode minimizes the far field effect. This catheter has a low noise level, thereby facilitating the recording of low- amplitude signals. However, the basket is not well-suited for mapping the papillary muscles, RV, or epicardium.

Although multielectrode mapping catheters provide a great advantage in the mapping process, the following limitations should be considered: mechanical trauma with frequent ectopy; transient injury of the superficial conduction bundles; limited maneuverability; lack of tissue contact information; and the potential for thrombus formation with the need for careful anticoagulation.

772

Multipolar catheters for high-resolution/high-density mapping

HD Grid Abbott



Flat sequential platform Cylinder shape electrode 2.53mm² surface area 1mm electrode 4mm spacing Able to chose bipoles

PentaRay Biosense



Cylinder shape 3.14mm² surface area 1mm electrode 2mm spacing Orion Boston scientific



Baloon plat form Flat electrode, Unidirectional 0.4mm² Surface area 1mm electrode 2.5mm spacing

Figure 3-6-3. Multipolar catheters for high-resolution/high-density mapping

775

773

776 **3-6-C.** Imaging

777 Magnetic resonance imaging (MRI)

778 Although the spatial resolution and quality of the 3D reconstructions are slightly poorer with MR angiography than 779 with multiple detector computed tomography (MDCT) angiography, CMR provides excellent soft tissue image 780 resolution and is widely regarded as the gold standard for imaging of the structural VT substrate. In addition to 781 providing a detailed assessment of cardiac morphology and function, CMR visualizes myocardial scars with a high 782 degree of precision⁷². MRI provides valuable information about the scar and grey zone areas, scar transmurality, 783 heterogeneity, and location, and it is able to visualize intramural and epicardial scars. The VT origin could be 784 identified within a hyper-enhanced LV scar region in 96% of cases⁷³. 785 In the atria, delayed enhanced MRI (DE-MRI) has been reported to characterize the atrial fibrosis in detail⁷⁴. Attempts

- to categorize the extent of fibrosis seem to be correlated with epidemiological variables and AF ablation outcomes⁷⁵.
- 787 DE-MRI may visualize the critical site of the reentrant circuit, which should be targeted for ablation.

788 MDCT imaging

- 789 High-quality pre-procedural imaging has two main goals: to gain a comprehensive understanding of the cardiac
- anatomy to identify any technical difficulties and to detect any potential risks⁷⁶.
- 791 Detailed anatomic variants of the size and shape of cardiac structures can be characterized. Sizing and location
- information (for example, in LA and PV) provided by 3D imaging may become even more important with the adventof complex ablation tools such as cryoballoons.
- 794 The anatomical interrelationship of extracardiac structures (esophagus, phrenic nerve, coronary arteries and the
- venous system, valve apparatus, epicardial fat, calcification, etc.) with cardiac chambers is important because of
- their vulnerability to ablative injury⁷⁷ A thrombus in the LA, LAA, and LV can be ruled out preprocedually^{78,79}. In
- 797 VT patients, scar characteristics can be observed as wall thinning in the scar region with the use of MDCT, which
- provides high spatial and temporal resolution⁸⁰. Intra-myocardial hypodensity and subepicardial "scalloping"
- provide additional information regarding hypoperfusion and (fibro-)fatty replacement⁸¹.

800 **3-6-D. Image integration**

- 801 Current ablation techniques are heavily reliant on EAM systems, which invasively create 3D reconstructions of
- 802 cardiac chambers (Carto, Biosense Webster, Inc; NAVX, St. Jude Medical; Rhythmia Mapping, Boston Scientific
- 803 Inc). Relying solely on EAM is associated with important limitations because EAM systems do not provide true
- anatomic imaging; instead, they derive 3D reconstructions from catheter– electrode contact at the myocardial
- 805 surface. To achieve high-resolution 3D images of the left cardiac geometry using conventional mapping systems,
- 806 the catheter has to be sequentially placed at many different sites in the chamber, which can be time-consuming and
- does not always show all anatomical details of the chamber, especially in anatomically abnormal patients.
- 808 Additionally, because contact with the catheter surface highly impacts the electro-anatomical information, and
- 809 because far-field and near-field effects cannot be negligent, there is potential to generate inaccurate data or errors of
- 810 the scar characteristics, especially in a ventricle.
- 811 Overall, EAM systems have the potential to underestimate or overestimate the extent of scars and arrhythmogenic
- 812 substrates. Therefore, real-time integration of preprocedural or intraprocedural imaging in EAM systems to guide
- 813 ablation procedures may provide an increasing interest. Integration of imaging data provides a more accurate
- 814 definition of the extent and distribution of the arrhythmogenic substrate. Furthermore, image integration provides
- 815 detailed anatomical information that allows us to manipulate a catheter more easily and in a safer manner.
- 816 At CHU Bordeaux, the preprocedural information can be implemented in a 3D model using the MUSIC platform
- 817 (CHU Bordeaux, LYRIC, INRIA) and exported as meshes that can be integrated in the 3D EMS to understand the
- 818 individual patient's disease and guide the approach and ablation. Figure 3-6-4 briefly summarizes the Music platform,
- 819 and an example is provided in **Figure 3-6-5**.



826

Figure 3-6-4. The MUSIC platform. All preprocedural information acquired from MDCT, DE-MRI, body surface mapping or other imaging is processed in the MUSIC platform. Different 3D meshes are made and exported as a .vtk or DIF model with color-coded wall thickness maps and scar and border zone maps. These meshes can be merged on the 3D EAM system to guide the ablation procedure.

MUSIC platform Image integration on the 3D-map



827 Figure 3-6-5. Various types of preprocedural imaging information and integration in the EAM system.

Patients with an inferior infarction. A. Color-coded wall thickness map created from MDCT data. B. Fat tissue distribution map from MDCT data. C.

829 Scar distribution from MDCT data. D. Scar distribution map from DE-CMR data. All maps can be integrated in the EAM system using the MUSIC
 830 platform.

831

832 **3-7. Aim of the thesis**

833 Conventional mapping techniques and modalities that have been used so far to clarify the mechanisms of scar-related 834 tachycardias are described herein. The aim of the thesis was to describe the impact of recent improvements in 835 mapping technology, especially high-resolution/high-density mapping systems and imaging, on ablation treatment. 836 The thesis has two main parts, the animal experimental part and the clinical study.

837 Recently, high-resolution/high-density mapping systems are being increasingly used in clinical situations, as 838 mentioned in the Introduction. As described in chapter 4, we analyzed the detailed effects of several factors involved 839 in catheter configuration on EGMs. First, using infarcted sheep and a high-density grid catheter, we endocardially 840 mapped the LV, collected the EGMs referencing MRI-guided scar and healthy areas, and analyzed the impact of inter-841 electrode spacing on local EGMs in scar, border, and healthy areas. Next, using a similar animal model with the same 842 catheter, we analyzed the impact of bipolar orientation compared with the activation direction on EGMs. Then, we 843 discussed the impact of inter-electrode spacing and bipolar orientation on the threshold to determine the scar. Finally, we analyzed the impact of the electrode size on EGMs. In the last study, we directly mapped the heart epicardially 844 845 with dedicated catheters with a different electrode size in sheep with a standard median sternotomy.

846 The clinical parts of the thesis are described in chapter 5 and chapter 6. In chapter 5, we elucidated the effectiveness of using the novel EAM system, RhythmiaTM, with the Orion catheter, which provides a map with the highest 847 848 resolution and highest density available so far. We mapped several forms of complex post-AF ATs using this system 849 to clarify the AT mechanisms and precise circuits of these ATs and to validate the accuracy of determining the critical 850 site for AT termination using this system. First, we revisited the anatomical MATs in post-AF ATs and elucidated the 851 detailed circuits of these ATs. Following the first study in this chapter, we also reported the complex circuits in 852 localized ATs, PV-related ATs, multiple-loop ATs, single-loop biatrial ATs, VOM-related ATs, and recurrent cases of 853 these post-AF ATs. Additionally, we focused on the detailed activation in the high-resolution and high-density map 854 and elucidated a simple mechanism to predict the termination and conversion of ATs. Finally, using Lumipoint 855 software, which includes the newest algorithm for the Rhythmia system, we performed a simple and quick assessment 856 to discriminate reentrant ATs from focal ATs.

857 Chapter 6 deals with the relationship between wall thickness distribution on CT imaging and substrate mapping on 858 the 3D EAM in ICM patients. First, we characterized the relationship between the regional myocardial WT as imaged 859 by MDCT and EGM amplitudes within the scar, including near-field and far-field components. We also clarified 860 which component is automatically considered by the mapping system according to the WT. Second, we analyzed the high-resolution activation map of VT created by the RhythmiaTM mapping system and compared the location of the 861 862 VT is thmus and wall thickness channels derived from MDCT. Finally, we compared two ablation strategies: the 863 LAVA elimination strategy and the CT channel ablation strategy. In a total of 214 consecutive patients who received 864 CA for ischemic VT, 25 patients with a CT channel-based ablation strategy and 25 with a LAVA ablation strategy, 865 were matched in a 1:1 ratio based on propensity scores, and acute and midterm results were compared.

867 Chapter 7 briefly provides a summary and perspectives of mapping technology.
869 870

4. Impact of bipolar configuration in the recent high-resolution/high density mapping catheter on the local electrograms

871

Several factors, such as catheter and electrode shapes⁸², electrode size⁶⁸, inter-electrode distance⁸³, filtering⁸⁴, tissue contact⁸⁵, bipole vs activation orientation^{86,87}, conduction velocity⁸² are known to affect the EGMs. However, not all of them are analyzed systematically with in-vivo study (many of them are assessed by computation programing). Following the recent improvement of catheter technology, we focus on the three factors which may be differently installed on the mapping catheters depending on each compnay providing them, and which may affect the EGMs. The fundamental concept between the catheter setting and EGMs should be understood when we perform high density/high resolution mapping with multipolar catheters.

879

880 4-1. Impact of electrode spacing on the local EGMs

881 Background and purpose of the study

High-density/high-resolution mapping are increasingly being used for substrate delineation. Multipolar catheters with smaller electrode and inter-electrode spacing offer faster and higher density/resolution map^{28,87,88} and be expected to be superior to those obtained using conventional ablation catheters. Identification of low-voltage area, and abnormal EGMs is mandatory to target ablation sites. However, EGMs may be different between the catatheter settings, and the impact of these factors on bipole EGMs in the ventricle has not been systematically examined. In this study, we aimed to delineate the effect of increasing inter-electrode spacing on local (far- and near- field) EGMs, with reference to scar regions defined by MRI.

889 Methods and Results

890 For the study, HD-Grid catheter (Abbott, Minneapolis, MN, USA, Figure 1A) was used, where we can select a 891 different bipolar pairs to create a given EGM. To assess the effect of bipolar spacing, specific configuration was 892 created using electrodes 1 to 5 in each spline (Figure 4-1). The 2-mm bipole pair (Bi-2, 2mm center to center, 1mm 893 edge-to-edge) was created from electrodes 1-2, 2-3, 3-4, and 4-5 in each spline, which was defined as the smallest 894 segment. Bi-2 was compared to the 4-mm bipole pair (Bi-4, 4mm center to center, 3mm edge-to-edge) created from 895 electrodes1-3 and 3-5 in each spline. We also used the 8-mm bipole pair (Bi-8, 8mm center-to-center, 7mm edge-to-896 edge) created from electrodes 1-5. (Figure 4-1). In each beat acquisition, EGMs created by 2, 4, and 8mm center-to-897 center spacing covering exactly the same site was compared; Four Bi-2 segments are compared with two Bi-4 and 898 one Bi-8 recordings. Unipolar- and bipolar-EGMs were filtered from 2-100 Hz, and 30-300 Hz, respectively.

899



900

901 Figure 4-1. Bipolar configuration on the HD-GridTM catheter MRI-image registration

902 The HD-Grid[™] catheter has eight 1-mm electrodes with 1-mm spacing (edge-to-edge) in each spline. HD-32 mounts 4-splines, and HD-56 mounts 7-903 splines. 2-mm bipole pair (center to center) (Bi-2), which covers one segment, is created from electrodes 1-2, 2-3, 3-4, and 4-5 in each spline. The 4-mm 904 bipole pair (Bi-4) is created from electrodes 1-3 and 3-5 in each spline. The 8-mm bipole pair (Bi-8), which covers one site, is created from electrodes 1-905 5 (A). MRI-image with MRI-defined scar and grey area (border area) is merged in the 3D mapping system (B).

906

907 **Results**

- 3591 segments in Bi-2 were free from local abnormal ventricular activities (LAVAs); 1630 segments were within
 the MRI-defined scar/border area. Among them, 172 (10.6%) segments in Bi-4, and 219 (13.4%) segments in Bi-8
 showed LAVAs. In contrast, LAVAs were identified in 1177 segments in Bi-2; 1118 segments were within the MRIdefined scar/border area. Among them, LAVAs were missed in 161 (14.4%) segments in Bi-4, and 409 (36.6%)
 segments in Bi-8.
- 913 In segments with LAVAs, median far-field voltage increased from 0.09[0.06-0.14]mV in Bi-2, to 0.16[0.10-0.24]mV
- 914 in Bi-4, and 0.28[0.20-0.42]mV in Bi-8 (P<0.0001). Median near-field voltage increased from 0.14[0.08-0.25]mV in
- 915 Bi-2, to 0.21[0.12-0.35]mV in Bi-4, and 0.32[0.17-0.48]mV in Bi-8 (P<0.0001). Median near/far-field voltage ratio
- 916 decreased from 1.67 in Bi-2, to 1.43 in Bi-4, and 1.23 in Bi-8 (P<0.0001). In the purely scarred area, median voltage
- 917 significantly (P<0.0001) increased from 0.13mV to 0.26mV in Bi-4, and 0.51mV in Bi-8. Adding the voltage of two
- 918 or four adjacent 2-mm bipoles (Bi-2) included in the corresponding Bi-4 or Bi-8 resulted in almost the same voltage
- 919 (R²=0.99, R2=0.98, respectively).
- 920

921 Summary and conclusion

922 The finding from the present study demonstrated that

| 923 | (1) Increased spacing may miss LAVA areas and also mistakenly identifying scar or normal tissue areas as having |
|-----|---|
| 924 | LAVAs. |
| 925 | (2) Generally, both far- and near- field voltage may increase as the spacing increases. However, near-field increase |
| 926 | may be less proportional. |
| 927 | (3) Near-field/far-field voltage ratio increases as the spacing decreases due to the predominant reduction of far-field |
| 928 | effect. |
| 929 | (4) In pure scar areas, local voltages were additively increased as the spacing increases, however local voltages in |
| 930 | the healthy tissue were more heterogenous. This may be because only far-field voltages are reflected in the pure scar |
| 931 | area, while both far- and near-field voltages are mixed in the healthy area. |
| 932 | We conclude that closer spacing is superior for identifying surviving tissue in the scar. Far-field voltage increases |
| 933 | additively with spacing while near-field voltages are more sensitive to the tissue heterogeneity. Near-field EGMs are |
| 934 | more easily identified with smaller spacing, particularly due to the reduction of far-field effect in scar. |
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| 939 | |
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Detailed Analysis of the Relation Between Bipolar Electrode Spacing and Far- and Near-Field Electrograms



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ABSTRACT

OBJECTIVES This study sought to evaluate the relation between bipolar electrode spacing and far- and near-field electrograms.

BACKGROUND The detailed effects of bipolar spacing on electrograms (EGMs) is not well described.

METHODS With a HD-Grid catheter, EGMs from different bipole pairs could be created in each acquisition. This study analyzed the effect of bipolar spacing on EGMs in 7 infarcted sheep. A segment was defined as a 2-mm center-to-center bipole. In total, 4,768 segments (2,020 healthy, 1,542 scar, and 1,206 in border areas, as defined by magnetic resonance imaging [MRI]) were covered with an electrode pair of spacing of 2 mm (Bi-2), 4 mm (Bi-4), and 8 mm (Bi-8).

RESULTS A total of 3,591 segments in Bi-2 were free from local abnormal ventricular activities (LAVAs); 1,630 segments were within the MRI-defined scar and/or border area. Among them, 172 (10.6%) segments in Bi-4 and 219 (13.4%) segments in Bi-8 showed LAVAs. In contrast, LAVAs were identified in 1,177 segments in Bi-2; 1,118 segments were within the MRI-defined scar and/or border area. Among them, LAVAs were missed in 161 (14.4%) segments in Bi-4 and in 409 (36.6%) segments in Bi-8. In segments with LAVAs, median far-field voltage increased from 0.09 mV (25th to 75th percentile: 0.06 to 0.14 mV) in Bi-2, to 0.16 mV (25th to 75th percentile: 0.10 to 0.24 mV) in Bi-4, and to 0.28 mV (25th to 75th percentile: 0.02 to 0.42 mV) in Bi-2, to 0.21 mV (25th to 75th percentile: 0.12 to 0.35 mV) in Bi-4, and to 0.32 mV (25th to 75th percentile: 0.17 to 0.48 mV) in Bi-8 (p < 0.0001). The median near-field voltage ratio decreased from 1.67 in Bi-2, to 1.43 in Bi-4, and 1.23 in Bi-8 (p < 0.0001).

CONCLUSIONS Closer spacing better discriminates surviving tissue from dead scar area. Although far-field voltage systematically increases with spacing, near-field voltages were more variable, depending on local surviving muscular bundles. Near-field EGMs are more easily observed with smaller spacing, largely due to the reduction of the far-field effect. (J Am Coll Cardiol EP 2019;5:66-77) © 2019 by the American College of Cardiology Foundation.

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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ipolar mapping of ventricular scar has previously been validated with both focal ablation catheters and multipolar catheters (1-3). Multipolar mapping is increasingly being used for substrate delineation. It offers a faster and higher density map (4-6) that is expected to be superior to that obtained using ablation catheters. However, the impact of interelectrode spacing on bipole electrograms (EGMs) in the ventricle has not been systematically examined. This seems particularly important because ablation targets are determined by the signal recorded during the mapping phase, whether it is an activation or voltage map. The aims of the present study were to delineate the effect of increasing interelectrode spacing on local (far- and near-field) EGMs, with reference to scar regions defined by magnetic resonance imaging (MRI).

SEE PAGE 78

METHODS

EXPERIMENTAL MYOCARDIAL INFARCTION. Experimental protocols were conducted in compliance with the Guiding Principles in the Use and Care of Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996). In addition, the study was approved by the institutional animal use and care committee, and conformed to the guide for the care and use of laboratory animals. Seven female sheep (age: 4.1 years; weight: 54.9 \pm 6.9 kg) were sedated with an intramuscular injection of ketamine hydrochloride (20 mg/kg), acepromazine (0.1 mg/kg), and buprenorphine (20 µg/kg). After an intravenous injection of propofol (2 mg/kg), the sheep were intubated, and anesthesia was maintained with 2% to 3% isoflurane. Sheep were ventilated with a respirator (CARESTATION/Carescape GE, Chicago, Illinois), using room air supplemented with oxygen. An intravenous catheter was placed in the internal jugular vein for infusion of drugs and fluids. Arterial blood gases were monitored periodically, and ventilator parameters were adjusted to maintain blood gases within physiological ranges. A sheep myocardial infarction model was created by an experienced invasive cardiologist using a selective ethanol injection (1 to 2 ml) in the distal one-third of the left anterior descending artery.

MRI MYOCARDIAL SCAR SEGMENTATION. Late gadolinium-enhanced cardiac MRI was performed 2 to 3 months after the creation of myocardial infarction. Image processing was performed by 2 trained technicians using MUSIC software (EQUIPEX MUSIC, Liryc, Universite de Bordeaux/INRIA, Sophia Antipolis, 67

ABBREVIATIONS AND ACRONYMS

EGM = electrocardiogram

LV = left ventricle

LAVA = local abnormal ventricular activity

MRI = magnetic resonance

imaging

VT = ventricular tachycardia

ELECTROPHYSIOLOGICAL STUDY AND MAPPING WITH HD-GRID CATHETER. Electrophysiological study with the HD-Grid catheter (Abbott, St. Paul, Minnesota) (Figure 1A) was performed 1 to 3 days after the MRI examination in surviving post-infarct sheep, with identical sedation, analgesia, intubation, and ventilation protocols for mapping of the scar using 3dimensional electroanatomical mapping (EnSite Precision system, Research Version, Abbott St. Paul, Minnesota) (Figure 1A). A diagnostic catheter (Quadripolar Inquiry, Abbott) was placed in the right ventricle and coronary sinus. The LV was mapped with the research-use HD-Grid catheter (3-mm interelectrode spacing and 1-mm electrode size) via a retrograde aortic approach and/or transseptal approach. A steerable long sheath (Agilis, Abbott) was used if required. The internal projection setting was set at 7 mm with 10-mm interpolation. Field-scaling was applied for all maps. On the point acquisition, contact with the LV endocardial surface was confirmed by fluoroscopy and by the proximity indicator on the EnSite Precision system. The research version of this system also includes 2 features to prove the contact; one feature was to show the catheter placement in each beat, and the other was to allow the system to display whether the multipolar catheter electrodes were in contact with the tissue based on the impedance information (Online Figure 1). The beat was not acquired when the catheter was distorted because it was trapped in a particular space (e.g., the papillary muscles, valves, trabeculations) or when adjacent 2 splines touched each other, which caused noises.

France). Segmentation was performed as

described previously (7,8). Briefly, the cardiac

chambers, ventricular epicardium, ascending

aorta, and coronary sinus were segmented

using semi-automatic methods (8). From left

ventricular (LV) wall segmentation, adaptive

histogram thresholding was applied to

segment dense scar (threshold set at 50%

maximum signal intensity) and the gray zone

(from 35% to 50%) (9-11).

For the registration, all segmentations of MRI imaging were exported as meshes and loaded into the EnSite system. The registration algorithm with the Ensite Fusion module allowed dynamic molding of the 3-dimensional electroanatomical geometry onto the MRI surface (12). After primary registration, the registered model was refined using a second set of fiducial points (e.g., left atrium, coronary sinus, aortic root, LV apex, and mitral annulus) judiciously placed in a stepwise fashion to further align both surfaces at sites of local mismatch (Figure 1B). 68 Takigawa et al. Impact of Bipolar Spacing on EGMs JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 5, NO. 1, 2019 JANUARY 2019:66-77



EGM ANALYSIS. With a HD-Grid catheter, different bipolar pairs could be selected. To assess the effect of bipolar spacing, a specific configuration was created using electrodes 1 to 5 in each spline (Figure 1A). The 2-mm bipole pair (Bi-2; 2 mm centerto-center, 1 mm edge-to-edge) was created from electrodes 1 to 2, 2 to 3, 3 to 4, and 4 to 5 in each spline, which was defined as the smallest segment. Bi-2 was compared with the 4-mm bipole pair (Bi-4; 4 mm center-to-center, 3 mm edge-to-edge) created from electrodes 1 to 3 and 3 to 5 in each spline. We also used the 8-mm bipole pair (Bi-8; 8 mm centerto-center, 7 mm edge-to-edge) created from electrodes 1 to 5 (Figure 1A). In each beat acquisition, EGMs created by 2-, 4-, and 8-mm center-to-center spacing that covered exactly the same site were compared; 4 Bi-2 segments were compared with 2 Bi-4 and 1 Bi-8 recordings. Bipolar EGMs were filtered at 30 to 300 Hz. HD-32 (4 splines) was used in sheep 1 to 5, and HD-56 (7 splines) was prepared for sheep 6 and sheep 7. Importantly, HD-32 and HD-56 have the same electrode spacing (and the same electrode size; the only difference is the number of splines). Again, each portion between adjacent electrodes on

the spline was defined as 1 segment, and the region covered between electrodes 1 and 5 was defined as 1 site (Figure 1B). We arbitrarily defined Bi-2 as the reference, and compared the following among 3 different bipolar spacings in each MRI-defined regions: 1) detection of local abnormal ventricular activities (LAVAs); 2) changes in EGMs at sites where far- and near-field potentials were separately measured; and 3) changes in single potentials in purely healthy and purely scar areas.

Our definition of LAVA has been described previously (5). LAVAs are defined as sharp, highfrequency ventricular potentials, possibly of low amplitude (but not always), that are distinct from the far-field ventricular EGMs. They sometimes display fractionation, double, or multiple components separated by very low-amplitude EGMs or an isoelectric interval, and are poorly coupled to the rest of the myocardium. In cases in which the discrimination of far- and near-field EGMs was difficult, programmed ventricular stimulation or local pacing with decremental output was performed. LAVA analysis was performed manually by 2 independent, blinded physicians.

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STATISTICAL ANALYSIS. Data are expressed as mean \pm SD and/or median (25th to 75th percentile) for normally distributed and skewed data, respectively. For the comparison of the 2 groups, Steel-Dwass analysis was performed. A p value <0.05 was considered statistically significant.

RESULTS

EGM ACQUISITION. EGMs were collected during sinus rhythm in 5 sheep and during right ventricular pacing in the remaining 2 because of frequent mechanical ventricular rhythm during sinus rhythm (Table 1). In total, 4,768 segments were analyzed by Bi-2, Bi-4, and Bi-8. A total of 2,020 segments were defined by MRI as a healthy area, 1,542 segments were in the MRI-defined scar area, and 1,206 segments were in the MRI-defined gray areas (border area).

OVERLOOKING TRUE SCARS WITH INCREASED BIPOLE SPACING. A total of 3,591 segments were free from LAVAs with Bi-2 (Figure 2A). Yet, in 181 (5.0%) segments analyzed with Bi-4 and 228 (6.3%) with Bi-8, LAVAs were recorded as a consequence of the larger antenna of the bipoles. In the MRI-defined scar area (Figure 2D), single component EGMs without LAVAs were identified in 818 segments with Bi-2. However, in 113 (13.8%) segments analyzed with Bi-4 and 116 (14.2%) segments with Bi-8, LAVAs were recorded for the same reason. In the MRI-defined border areas (Figure 2C), 812 segments were free from LAVAs in Bi-2, of which 59 (7.3%) segments in Bi-4 and 103 (12.7%) segments in Bi-8 showed LAVAs. In the MRI-defined healthy areas (Figure 2A), 1,961 segments were free from LAVAs with Bi-2, of which 9 (0.5%) segments with Bi-4 and 9 (0.5%) segments with Bi-8 showed multiple components.

OVERLOOKING LAVAS WITH INCREASED BIPOLE SPACING, LAVAs were identified in 1.177 segments in Bi-2 (Figure 3A). Two hundred two (17.2%) of these segments in Bi-4 and 449 (38.1%) in Bi-8 missed these LAVAs. In the MRI-defined scar areas (Figure 3D), LAVAs were identified in 724 segments with Bi-2. Seventy-nine (10.9%) of these segments in Bi-4 and 236 (32.6%) segments in Bi-8 missed these LAVAs. In the MRI-defined border areas (Figure 3C), LAVAs were identified in 394 segments in Bi-2. One hundred (25.4%) of these segments in Bi-4 and 173 (43.9%) segments in Bi-8 missed these LAVAs. In the MRIdefined healthy areas (Figure 3A), multiple component EGMs were identified in 59 segments in Bi-2, mostly around the mitral valve, whereas 23 (39.0%) of these segments in Bi-4 and 40 (67.8%) segments in Bi-8 showed single component potentials.

| Sheep # | Sex | Age (yrs) | Weight (kg) | Rhythm | HD Grid | Analyzed Site | Analyzed Segments |
|------------|-----|--------------|----------------|--------------|---------|------------------|----------------------|
| 1 | F | 5 | 60 | Sinus | HD-32 | 156 | 624 |
| 2 | F | 5 | 56.5 | Sinus | HD-32 | 140 | 560 |
| 3 | F | 5 | 60 | Sinus | HD-32 | 192 | 768 |
| 4 | F | 5 | 48 | Sinus | HD-32 | 136 | 544 |
| 5 | F | 5 | 63 | Sinus | HD-32 | 116 | 464 |
| 6 | F | 2 | 52 | RV pacing | HD-56 | 154 | 616 |
| 7 | F | 2 | 44.6 | RV pacing | HD-56 | 298 | 1,192 |

NEAR-FIELD/FAR-FIELD VOLTAGE RATIO DECREASES WITH SPACING. In total, 1.177 segments in Bi-2, 1.156 segments in Bi-4, and 956 segments in Bi-8 showed both far-field and near-field EGMs. In general, the mean far-field voltage significantly increased as the spacing increased (Figure 4A[a]) (p < 0.0001). The tendency was similar in the MRI-defined healthy area, the MRI-defined border area, and the MRI-defined scar area (Figures 4B[a], 4C[a], and 4D[a]). In general, mean near-field voltage became significantly larger as the spacing increased (Figure 4A[b]) (p < 0.0001), but the extent of the increase was smaller than the far-field voltage, and the far-field voltage showed more proportional increases with the spacing. The increase did not reach significance in Bi-2 versus Bi-4 and Bi-4 versus Bi-8 in the MRI-defined border area (Figure 4C[a]).

In general, the mean near-field/far-field voltage ratio significantly decreased as the spacing increased (Figure 4A[c]) (p < 0.0001). The tendency was similar in the MRI-defined border and scar areas (Figure 4C[c] and 4D[d]).

RELATION BETWEEN SPACING AND VOLTAGE IN PURELY HEALTHY AND PURELY SCARRED AREAS. We defined 1,856 segments as purely healthy where electrodes 1 to 5 in 1 spline were all simultaneously in an MRI-defined healthy area, without LAVAs. We defined 228 segments as purely scarred where electrodes 1 to 5 in 1 spline were all simultaneously in an MRI-defined scar area without LAVAs.

In the purely scarred area, the median voltage significantly (p < 0.0001) increased from 0.13 to 0.26 mV in Bi-4 and to 0.51 mV in Bi-8 (Figure 5A). Adding the voltage of 2 or 4 adjacent 2-mm bipoles (Bi-2) included in the corresponding Bi-4 or Bi-8 resulted in almost the same voltage ($R^2 = 0.99$, $R^2 = 0.98$, respectively) (Figures 5B and 5C).

In the purely healthy area, median signal voltage increased from 1.18 mV in Bi-2 to 1.81 mV in Bi-4, and

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to 2.58 mV in Bi-8 (Figure 6A). Adding the voltage of 2 or 4 adjacent 2-mm bipoles (Bi-2) included in the corresponding Bi-4 or Bi-8 was more weakly correlated to the voltage in Bi-4 ($R^2 = 0.82$) and Bi-8 ($R^2 = 0.64$) (Figures 6B and 6C).

DISCUSSION

MAJOR FINDINGS. In the present study, we examined EGMs in the same beat with the different spacing bipolar pairs and demonstrated the following findings. 1) Widely spaced bipoles might fail to discriminate the local tissue characteristics; increased spacing might result in missing LAVA areas and in mistakenly identifying scar or normal tissue areas as having LAVAs. 2) Although, generally, both far- and near- field voltage might increase as the spacing increases, a near-field increase might be less proportional. 3) The near-field/far-field voltage ratio increased as the spacing decreased due to the predominant reduction of far-field effect. 4) In pure scar areas, local voltages were additively increased as the spacing increased; however, local voltages in the healthy tissue were more heterogenous.

LAVA DETECTION ACCURACY WITH BIPOLAR SPACING. In the present study, we demonstrated that LAVA potentials detected by the closest spacing (Bi-2) might be missed in Bi-4 by 17.2% and by 38.1% in Bi-8. This false-negative rate was generally higher in the MRI-defined border area than that in the dense scar area. LAVA timing was reported to be earlier in the JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 5, NO. 1, 2019 JANUARY 2019:66-77



G13 [0.31 mV] +G35 [0.36 mV], and so on). Abbreviations as in Figures 1 and 2.

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in a healthy area. Abbreviations as in Figures 1 and 2.

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border zone than that in the dense scar area (13), and early LAVA in sinus rhythm might be associated with channels entering into the scar (14). In these border zones, far-field EGMs were larger due to adjacent healthy tissue. With widely spaced bipoles, some LAVAs detected with Bi-2 might be masked, and therefore, might be missed by large far-field EGMs (Figure 3E).

In contrast, when single potentials were detected with the smallest bipolar spacing (Bi-2), 5% with Bi-4 and 6% with Bi-8 had LAVAs with far- and near-field EGMs, particularly in the MRI-defined scar areas, where the incidence of LAVAs increased to 13.8% by Bi-4 and to 14.2% by Bi-8. This did not suggest that larger spacing bipoles detected LAVAs better, but rather that widely spaced bipoles indiscriminately detected LAVA EGMs across the entire bipole, which smaller bipole pairs were able to pinpoint more accurately (Figure 2E). Even if larger bipoles are not as accurate as smaller ones, they may still be useful, for example, in identifying an interesting EGM that is nearby but which is not right under the spline.

VOLTAGE CHANGES IN FAR- AND NEAR-FIELD POTENTIALS. Two previous studies demonstrated that bipolar voltages, in general, increase with spacing (13,14). However, neither study compared identical sites simultaneously, nor did they discriminate between near-field and far-field EGMs (15,16). Furthermore, the comparison between different catheters might have affected the results because of the different electrode sizes and shapes (16). In the present study, by comparing EGMs with a different spacing at exactly the same location (site) and beat, the exact effect of bipolar spacing was clearly described. We demonstrated that both far- and nearfield voltages generally increased with spacing, and that this rule was generally consistent in the MRIdefined scar and border areas. However, the voltage increased more in far-field EGMs with longer spacing; thus, the near-field/far-field voltage ratio decreased, which resulted in worse discrimination between nearfield and far-field EGMs

CORRELATION BETWEEN BIPOLAR SPACING AND VOLTAGE. In purely scarred areas, the additive voltage of Bi-2 was equal to the voltages of Bi-4 and Bi-8 with a good correlation. The (electrode center-tocenter) spacing might be additively associated with far-field voltages, and the correlation coefficient was very high. In contrast, in purely healthy areas, although there was a correlation between the additive voltage of the smallest bipolar spacing (Bi-2) and the other spacing, the correlation coefficient was not as directly proportional as in the purely scarred area. This discrepancy might be because of the fact that single components in the purely scarred area might represent the pure far-field EGMs, whereas single component EGMs in the purely healthy areas might represent both far-field and near-field components, which would not simply be summed over a longer bipole.

In segments where both far- and near-field EGMs were identified, far-field EGMs tended to increase with spacing. However, the extent was not as directly proportional as in the completely scarred areas. This might be due to the presence of some near-field component in the far-field signal. Another hypothesis was that in the border zone, the far-field effect could be produced both from the horizontal direction and the vertical direction (subendocardial surviving tissues), whereas in the complete scar zone, the farfield effect from the vertical direction might be less.

The change in the near-field voltages according to bipolar spacing was less proportional compared with the far-field EGMs, especially in the border zone. In some cases, the voltages were similar even when the spacing was increased (Figure 2E). If there was only a single piece of surviving muscle, covered by 1 segment with Bi-2, this signal voltage might not change dramatically in Bi-4 or Bi-8 when the other segments were all scar. However, when the surviving muscular bundle was large enough to extend beyond a single 2-mm segment, the near-field signal would increase with a longer bipolar spacing. In addition, the near-field voltage was more sensitive to the relationships among bipolar orientation, tissue orientation, and activation direction, which could affect the near-field EGMs more (17).

CLINICAL IMPLICATIONS. Mapping during ventricular tachycardia (VT) can be performed in only 30% to 40% of cases (18). Therefore, detection and characterization of myocardial scar during sinus rhythm may be a prerequisite for substrate-based scar modification in some patients. For this substrate-based scar modification, several techniques have been reported, such as scar de-channeling (19), late potential ablation (20), scar homogenizing (21), and LAVA elimination (5). In all of these techniques, residual abnormal muscle bundles in the scar that are potentially associated with the initiation or maintenance of VT are targeted. These tissues usually have small, sharp EGMs, which are occasionally masked by the far-field component (5). Detection and discrimination of these near-field EGMs from the far-field EGMs is mandatory for these techniques. We demonstrated

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that catheters with smaller bipolar spacing might achieve the precise discrimination of the local tissue structures. In addition, we elucidated the impact of bipolar spacing on both far- and near-field EGMs. Recently, industry has provided new technologies, including several types of multipolar mapping catheters with different electrode size and different interelectrode spacing (e.g., PentaRay, electrode size: 3.14 mm², center-to-center interelectrode spacing: 3 mm; Biosense-Webster Inc., Diamond Bar, California; and Orion™, electrode size: 0.4 mm², center-to-center interelectrode spacing: 2.5 mm; Boston Scientific, Marlborough, Massachusetts). Although larger electrode and larger inter-electrode spacing might increase the far-field effect, the impact on the EGMs in these different technologies should be examined. In addition, a specific scar threshold should be determined in each different catheter platform, although <0.5 and >1.5 mV have been, so far, generally used for the threshold of dense scar and healthy voltages, respectively.

STUDY LIMITATIONS. First, LAVA analysis was performed manually. To minimize bias when identifying LAVAs, analysis was performed by 2 independent, blinded physicians with adjudication by a third physician when there was disagreement. Second, contact force is known to affect recorded EGMs, but no multipolar mapping catheters were capable of contact force measurement. Intracardiac echocardiography might be a better method to minimize this limitation. Third, although histology and pathology were not compared with the MRIdefined scar in the present study, the well-known cutoff of MRI-defined scar was used for the analysis (9-11). Fourth, because EGMs during sinus rhythm and right ventricular pacing were mixed for the analysis, local voltages might have been affected. Finally, this study did not include epicardial mapping, which might have resulted in different EGM characteristics due to the impact of epicardial fat.

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CONCLUSIONS

Closer spacing is superior for identifying surviving tissue in the scar. Far-field voltage increases additively with spacing, whereas near-field voltages are more sensitive to the tissue heterogeneity. Near-field EGMs were more easily identified with smaller spacing, particularly due to the reduction of the farfield effect in scar.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Highresolution mapping with smaller spacing provides a more accurate characterization in the infarcted scar associated with the VT substrate. Better understanding of the substrate will provide the appropriate ablation strategy without unnecessary radiofrequency applications. Understanding of the effect of interelectrode spacing on both far- and near-field EGMS must be required in the era when the advancing technology in the industry might provide different types of catheters.

TRANSLATIONAL OUTLOOK 1: Although the high-resolution mapping catheter will certainly provide more precise characteristics of substrates of VT, the clinical impact should be examined in further studies.

TRANSLATIONAL OUTLOOK 2: Lack of contact force in mapping catheters may limit the advantage of high-resolution mapping system. A larger bipole, but with contact force versus a smaller bipole without contact force, should be examined.

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KEY WORDS electrograms, high-density mapping, LAVA, multipolar catheters

APPENDIX For a supplemental figure, please see the online version of this paper.

4-2. Impact of bipolar orientation vs. activation direction on the local EGMs.

960 **Background and purpose of the study**

- Statistically derived low-voltage threshold of <1.5 mV⁵⁵, and dense scar threshold of <0.5mV have been widely used.
 And these low voltage areas are targeted for substrate ablation for VT. However, not only the electrode size and
- 963 spacing^{61,67} but also the activation wavefront relative to the catheter orientation will influence the local voltage⁸⁹.
- However, the influence on the local EGMs of the activation wavefront relative to the bipole pair has not been closely
- 965 examined. In this study, we aimed to delineate the impact of the activation wavefront direction on the local EGMs in
- 966 terms of both the voltage and LAVAs.

967 Methods and results

- 968 We used the same mapping system, catheter, and animal models. We examined 7 surviving post-infarct sheep. This
- time, we selected eighteen diagonally orthogonal electrode pairs in total across all splines and bipolar EGMs from
- 970 each pair of opposing electrodes were compared (eg. A1-B3 [south-east (SE) direction] vs. A3-B1 [north-east (NE)
- 971 direction] is a diagonally orthogonal bipolar pair, similarly A3-B5 vs. A5-B3..., and C5-D7 vs. C7-D5). By selecting
- 972 these configurations, EGMs at particular locations were analyzed comparing the diagonally orthogonal bipolar pairs.
- 973 Unipolar- and bipolar-EGMs were filtered from 2-100 Hz, and 30-300 Hz, respectively.



974

975 Figure 4-2. MRI registration and 3D-anatomical mapping with HD-32 GridTM catheter

976 MRI-image with MRI-defined scar and grey zone (border zone) was merged on the 3D mapping system. Voltage maps using only configuration of north-977 east [NE] direction and only that of south-east [SE] direction created from the reference acquisition displayed the difference distribution of the low-978 voltage area HD-32 GridTM catheter is composed of 32 of 1-mm ring electrodes, and any two electrodes can be selected to create bipolar EGMs. 18 979 diagonally orthogonal electrode pairs across splines (ex. A1-B3 [SE direction, red two-way arrow] vs. A3-B1 [NE direction, blue two-way arrow], A3-980 B5 vs. A5-B3...., and C5-D7 vs. C7-D5) were selected to assess each particular site (yellow dot) (A). EGMs displayed with NE and SE direction on the 981 4 sites ((a)-(d)) in the scar border are shown (B). 982

983 **Results**

- 4084 EGMs (one in each direction) were analyzed for 2042 sites (544 infarcted area, 488 border area, and 1010
- normal area). The higher- and lower-voltages measured by each pair of opposing electrodes significantly differed
- 986 (1.10mV[0.43mV-2.56mV] vs. 0.69mV[0.28mV-1.58mV], P<0.0001), and the median variation was
- 987 0.28mV[0.11mV-0.80mV] (31.7%[16.0%-48.9%]). The median voltage variation was significantly larger in MRI-
- 988 defined border area (36.0% [17.8%-51.3%]) compared to the other area (30.8% [15.3%-48.2%]) (P<0.003). The
- 989 voltage variation was maximized to 48.7%[37.7-61.6%] (P<0.0001) on sites where the activation front was
- 990 perpendicular to the one bipolar direction and parallel to the other.
- LAVAs were detected in 592/2042 (29.0%) in total, frequently distributed in the border area. 177 (29.9%) of LAVAs
- 992 were missed with one direction and 180 (30.4%) in the other. When the LAVAs detected by NE (n=415) are defined
- 993 as the reference, 235/415 (56.6%) matched with the SE.
- 994

995 Summary and conclusion

- In the present study, we examined the bipolar EGMs on the same location with diagonally orthogonal bipolar pairsand demonstrated the following findings.
- (1) Bipolar pair direction strongly impacts the assessment of local voltage, and the voltage variation between largerand smaller voltages was approximately 30%.
- 1000 (2) This variation was significantly larger in the MRI-defined border area, and maximized on the site where the 1001 activation front faced orthogonally to the one bipolar pair and parallel to the other.
- (3) Bipolar pair direction also impacts the detection of LAVA potentials, and LAVA distribution in one directionmisses at least 30% of LAVAs.
- 1004 In the present study, we underscore the significance of activation direction to the bipolar pair regarding the assessment
- 1005 of both the local voltages and the LAVAs, which may significantly influence the substrate mapping in VT ablation.
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- 1007
- Manuscript is in publication; Heart Rhythm. 2018 Dec;15(12):1853-1861. doi: 10.1016/j.hrthm.2018.07.020. Epub
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BACKGROUND The direct effect of bipolar orientation on electrograms (EGMs) remains unknown.

OBJECTIVE The purpose of this study was to examine the variation of EGMs with diagonally orthogonal bipoles.

METHODS The HD-32 Grid catheter (Abbott, Minneapolis, MN) can assess the effect of bipolar orientation while keeping the interelectrode distance and center unchanged. Seven sheep with anterior myocardial infarction were analyzed using diagonally orthogonal electrode pairs across splines by comparing local EGMs from each pair of opposing electrodes {eg. A1-B3 (southeast direction [SE]) vs A3-B1 (northeast direction [NE])}.

RESULTS A total of 4084 EGMs (1 in each direction) were analyzed for 2042 sites (544 in the infarcted area, 488 in the border area, and 1010 in the normal area). The higher and lower voltages measured using each pair of opposing electrodes significantly differed (1.10 mV [0.43–2.56 mV] vs 0.69 mV [0.28–1.58 mV]; P < .0001), and the median variation was 0.28 mV (0.11–0.80 mV) (31.7% [16.0%–48.9%]). The voltage variation was maximized to 48.7% (37.7%–61.6%) (P < .0001) on sites where the activation wavefront

was perpendicular to the one bipolar direction and parallel to the other. A total of 594 of 719 (82.6%) sites with the voltage <0.5 mV and 539 of 699 (77.1%) sites with the voltage >1.5 mV in NE stayed in the same voltage range as those in SE. However, only 348 of 624 (55.8%) sites with the voltage 0.5–1.5 mV in NE stayed in the same range as those in SE. Local ventricular abnormal activities (LAVAs) were detected in 592 of 2042 (29.0%) sites in total, frequently distributed in the border area. A total of 177 (29.9%) LAVAs were missed in one direction and 180 (30.4%) in the other. When 415 (70.1%) LAVAs detected in NE are defined as the reference, 235 of 415 (56.6%) matched with those detected in SE.

CONCLUSION The bipolar voltage and distribution of LAVAs may differ significantly between diagonally orthogonal bipolar pairs at any given site.

KEYWORDS Electrograms; Infarction; LAVA; Mapping; Multipolar catheters; Voltage

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Introduction

Detection and characterization of myocardial scar is a prerequisite for substrate-based scar modification during sinus

rhythm because mapping during ventricular tachycardia (VT) can be performed in only 30%–40% of cases.^{1,2} Bipolar voltage mapping has been correlated with dense

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scar defined by histopathology and magnetic resonance imaging (MRI) and has been universally implemented in clinical practice with a statistically derived low-voltage threshold of < 1.5 mV.^{3,4} Not only the electrode size and spacing^{5,6} but also the activation wavefront relative to the catheter orientation will influence the local voltage.⁷

However, the influence on the local electrograms (EGMs) of the activation wavefront relative to the bipolar pair has not been closely examined. The aims of the present study were to delineate the effect of the activation wavefront direction on the local EGMs in terms of both the voltage and local ventricular abnormal activities (LAVAs).

Methods

Myocardial infarction in experimental animal models

Experimental protocols were conducted in compliance with the Guiding Principles in the Care and Use of Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996). Moreover, the study was approved by the Institutional Animal Care and Use Committee in addition to conforming to the Guide for the Care and Use of Laboratory Animals. Seven female sheep (age 4.1 years; weight 54.9 \pm 6.9 kg) were sedated with an intramuscular injection of ketamine hydrochloride (20 mg/kg), acepromazine (0.1 mg/kg), and buprenorphine (20 µg/kg). After the intravenous injection of propofol (2 mg/kg), sheep was intubated and anesthesia was maintained with 2%-3% isoflurane. Sheep were ventilated with the respirator (CARESTATION/Carescape, GE Healthcare, Chicago, IL) using room air supplemented with oxygen. An intravenous catheter was placed in the internal jugular vein for infusion of drugs and fluids. Arterial blood gases were monitored periodically, and ventilator parameters were adjusted to maintain blood gases within physiological ranges. A sheep myocardial infarction model was created by an experienced invasive cardiologist using selective ethanol injection (1-2 cm³) in the distal one-third of the left anterior descending artery.

Myocardial scar segmentation from MRI

Late gadolinium–enhanced cardiac MRI was performed 2–3 months after the creation of the sheep myocardial infarction model. Image processing was performed by 2 trained technicians using the MUSIC software (Equipex MUSIC, Liryc institute, Université de Bordeaux/INRIA, Sophia Antipolis, France). Segmentation was performed as described previously.^{8,9} Briefly, cardiac chambers, ventricular epicardium, ascending aorta, and coronary sinus (CS) were segmented using semiautomatic methods.⁹ From the segmented left ventricular (LV) wall, adaptive histogram thresholding was applied in order to segment dense scar (threshold set at 50% of maximum EGM intensity) and gray zone (from 35% to 50%).¹⁰

Electrophysiology study and mapping with the HD-32 Grid catheter

Electrophysiology study with the HD-32 Grid catheter (Abbott, Minneapolis, MN) was performed 1-3 days after the MRI examination in surviving postinfarct sheep with an identical sedation, analgesia, intubation, and ventilation protocol used for mapping of the scar with a 3-dimensional electroanatomic mapping (3D-EAM) system (NavX Precision™ system, research version, Abbott). A diagnostic catheter (quadripolar, Inquiry, Abbott) was placed in the right ventricle (RV) and CS. The LV was mapped with the HD-32 Grid catheter (3-mm interelectrode spacing and 1-mm electrode size) via a retrograde aortic approach and/or transseptal approach. A steerable long sheath (Agilis, Abbott) was used, if required. The internal projection setting was set at 7 mm with 10 mm interpolation. Field scaling was applied for all maps. On the point acquisition, contact to the LV endocardial surface was confirmed by fluoroscopy and the proximity indicator on the NavX system.

For the MRI registration, all MRI-defined healthy, scar, and gray zone tissue segmentations were exported as meshes and loaded into the NavX system. The nonrigid registration algorithm with the Ensite[™] Fusion[™] module allowed warping of the 3D-EAM geometry onto the MRI surface.¹¹ After primary registration, the registered model was refined using a second set of fiducial points, such as left atrium, CS, aortic root, LV apex, and mitral annulus, judiciously placed in a stepwise fashion to further align both surfaces at sites of local mismatch (Figure 1A).

EGM analysis

With the HD-32 Grid catheter, an electrode pair can be selected to create a bipolar EGM representing the mapping point location to lie at the midpoint of the electrode pair, as shown in Figure 1B. Eighteen diagonally orthogonal electrode pairs in total across all splines were selected, and bipolar EGMs from each pair of opposing electrodes were compared {eg, A1-B3 (southeast [SE] direction) vs A3-B1 (northeast [NE] direction) is a diagonally orthogonal bipolar pair, and similarly A3-B5 vs A5-B3... C5-D7 vs C7-D5}. By selecting these configurations, EGMs at particular locations were analyzed by comparing the diagonally orthogonal bipolar pairs. EGMs were carefully excluded when the HD-32 Grid catheter was distorted on the surface and/or those suspected of noise or artifacts. Bipolar EGMs were filtered from 30 to 300 Hz, and voltages were automatically analyzed using the peak-to-peak voltages.

Definition

Sites with bipolar voltage <0.5, 0.5–1.5, and >1.5 mV was defined as dense scar area, low voltage area, and normal voltage area, respectively. In contrast, MRI-defined scar area, MRI-defined border area (gray zone), and MRI-defined healthy area were classified. Our definition of LAVA has been described previously.¹² LAVAs are defined



Figure 1 Magnetic resonance imaging (MRI) registration and 3-dimensional (3D) anatomic mapping with the HD-32 Grid catheter. A: The MRI image with MRI-defined scar and gray areas (border zone) was merged on the 3D mapping system. Voltage maps using only the configuration of the northeast (NE) direction and only that of the southeast (SE) direction created from the reference acquisition displayed the difference distribution of the low voltage area. B: The HD-32 Grid catheter is composed of 32 of 1-mm ring electrodes, and any 2 electrodes can be selected to create bipolar EGMs. Eighteen diagonally orthogonal electrode pairs across splines (ex. A1-B3 [SE direction, *red 2-way arrow*] vs A3-B1 [NE direction, *blue 2-way arrow*], A3-B5 vs A5-B3..., and C5-D7 vs C7-D5) were selected to assess each particular site (*vellow dot*).

as sharp high-frequency ventricular potentials, possibly of low amplitude (but not always), distinct from the far-field ventricular EGM. They sometimes display fractionation, double, or multiple components separated by very low amplitude EGMs or an isoelectric interval and are poorly coupled to the rest of the myocardium. In case the discrimination of far- and near-field EGMs was difficult, programmed ventricular stimulation or local pacing with decremental output was performed. LAVA analysis was performed manually by 2 independent blinded physicians.

Statistical analysis

Data are expressed as mean \pm standard deviation and/or [median; 25th–75th percentile] for normally distributed and skewed data, respectively. According to the skewness, the

 Table 1
 Baseline characteristics (N = 7)

 χ^2 test or Fisher exact test was used for categorical variables and an analysis of variance analysis or Kruskal-Wallis test was used for continuous variables. *P* values <.05 were considered statistically significant.

Results

EGM acquisition

EGMs were collected during sinus rhythm in 5 sheep and RV pacing in the remaining 2 because of frequent mechanical ventricular rhythm during sinus rhythm (Table 1). In total, EGMs on the 2042 locations were recorded by diagonally orthogonal bipolar pairs; 544 locations were in the MRI-defined scar area, 488 locations were in the MRI-defined border area (gray zone), and the remaining 1010 locations were in the MRI-defined nonscar area.

| Sheep no. | Sex | Age (y) | Weight (kg) | Rhythm | Total points | Used location | Bipolar EGM recordings |
|-----------|-----|---------|-------------|-----------|--------------|---------------|------------------------|
| 1 | F | 5 | 60 | Sinus | 2040 | 231 | 462 |
| 2 | F | 5 | 56.5 | Sinus | 1400 | 205 | 410 |
| 3 | F | 5 | 60 | Sinus | 1920 | 288 | 576 |
| 4 | F | 5 | 48 | Sinus | 1360 | 204 | 408 |
| 5 | F | 5 | 63 | Sinus | 1160 | 174 | 348 |
| 6 | F | 2 | 52 | RV pacing | 1260 | 261 | 522 |
| 7 | F | 2 | 44.6 | RV pacing | 3600 | 679 | 1358 |

EGM = electrogram; F = female; RV = right ventricular.



Figure 2 A: Voltage variation between the higher and lower voltages in diagonally orthogonal bipolar pairs examining the same local site. B: A subanalysis was performed to compare the voltage variation rate between the site where unipolar activation was perpendicular to one bipolar pair and parallel to the other orthogonal pair and the other sites.

Variation between higher and lower voltages in each location

The variation between higher and lower voltages in diagonally orthogonal bipolar pairs is shown in Figure 2A. Overall, the median voltage variation between orthogonal pairs was 0.28 mV (0.11-0.80 mV). In the MRI-defined healthy areas, the median voltage variation between orthogonal pairs was 0.72 mV (0.30-1.33 mV). In the MRI-defined border areas, the median voltage variation between orthogonal pairs was 0.16 mV (0.07-0.29 mV). In the MRI-defined scar areas, the median voltage variation between orthogonal pairs was 0.13 mV (0.06–0.26 mV). The median voltage variation was ~30%, but significantly greater in the MRI-defined border areas (36.0% [17.8%–51.3%]) than that in other areas (30.8% [15.3%–48.2%]) (P < .003).

Comparison of EGMs between bipolar pairs, parallel and orthogonal to the activation wavefront

In 108 of 2042 locations, we could identify that the unipolar activation wavefront, which was computed from the local activation time on the unipolar EGMs with maximum dV/dt, was orthogonal to one bipolar pair configuration and parallel to the

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Figure 3 Voltage range change between bipolar pairs in the northeast (NE) direction (ex. A3-B1) to those in the southeast (SE) direction (ex. A3-B1): (A) in total, (B) magnetic resonance imaging (MRI)-defined healthy area, (C) MRI-defined border area, and (D) MRI-defined scar area.

other (Figure 2B). In these sites located in the healthy area, the median voltage variation between higher and lower voltages in diagonally orthogonal bipolar pairs is 48.7% (37.7%–61.6%), which was significantly greater (P < .0001) than that in other locations (median 31.0% [15.5%–48.1%]) where the bipolar pairs were not orthogonal or parallel to the activation wavefront.

Voltage range change between diagonally orthogonal pairs

The behavior of voltage variation between the NE direction and the SE direction is shown in Figure 3. In total, 594 of 719 (82.6%) sites with the voltage <0.5 mV (dense scar area) in the NE direction stayed in the same voltage range as those in the SE direction and 539 of 699 (77.1%) sites with the voltage >1.5 mV (normal voltage area) in the NE direction stayed in the same voltage range as those in the SE direction. However, only 348 of 624 (55.8%) sites with the voltage 0.5–1.5 mV (low voltage area) in the NE direction stayed in the same voltage range as those in the SE direction.

In the MRI-defined healthy areas, 522 of 668 (78.1%) sites with the voltage >1.5 mV (normal voltage areas) stayed in the normal voltage range in the SE direction. Ten sites were in the low voltage area (<0.5 mV) in both bipolar directions, all of which were near the mitral valve.

In the MRI-defined scar areas, 316 of 378 (83.6%) sites with the voltage <0.5 mV (dense scar areas) stayed in the same voltage range in the SE direction. Five sites showed normal voltages even in the MRI-defined scar areas because of both far- and near-field contributions to the overall EGM. In all areas, sites in the voltage range 0.5-1.5 mV frequently shifted to other voltage ranges. In the MRIdefined healthy areas, they frequently moved to the voltage range >1.5 mV, and in the gray and scar areas, they frequently moved to the voltage range <0.5 mV.

LAVA detection

LAVAs were detected in 592 of 2042 (29.0%) EGMs in total. Most were distributed in the MRI-defined gray and scar areas (Figure 4A). Although the same location was examined using each pair of opposing electrodes, 177 of 592 (29.9%) LAVAs were only detected in SE (missed in NE) and 180 of 592 (30.4%) were detected in NE (missed in SE). Only 235 of 592 (39.7%) LAVAs were identified in both the diagonally orthogonal pairs (Figure 4B). When LAVAs detected in the NE direction is defined as the reference, 235 of 415 (56.6%) matched with those in the SE direction. The effect of the bipolar direction change is demonstrated in Figure 5.

At 235 sites where LAVAs were detected in both NE and SE directions, the median voltage variation between the higher and lower values was 33.3% (15.9%–48.2%) in the far-field EGMs and 25.0% (8.5%–50.0%) in LAVAs (near-field EGMs), as shown in Figure 6. Although the variation from the higher to the lower voltage was significantly greater in the far-field EGMs (P < .0001), it was more deviated in the near-field EGMs.

Discussion Major findings

In the present study, we examined the bipolar EGMs on the same location by using diagonally orthogonal bipolar pairs



Figure 4 A: Local ventricular abnormal activity (LAVA) distribution in each magnetic resonance imaging–defined area. B: LAVA detection rate. NE = northeast; SE = southeast.

and demonstrated the following findings: (1) Bipolar pair direction strongly affects the assessment of the local voltage. (2) The voltage variation was significantly greater in the MRI-defined border area and when the activation wavefront faced orthogonally to the one bipolar pair and parallel to the other. (3) Approximately 80% of the EGMs in the normal voltage range (>1.5 mV) in the MRI-defined healthy areas and in the dense scar range (<0.5 mV) in the MRI-defined scar areas remained in the same voltage range while being analyzed by using the diagonally orthogonal bipolar pair. (4) Half of the EGMs in the low voltage range (0.5–1.5 mV) are shifted to

a different voltage range, regardless of the local MRIdefined scar assessment, while being analyzed by using the diagonally orthogonal bipolar pair. (5) Bipolar pair direction also affects the detection of LAVA potentials, and LAVA distribution in 1 direction misses at least 30% of LAVAs.

Effect of the direction of the bipolar pair on the local voltage

The effect of the activation direction on the local EGMs was previously reported.^{7,13} Brunckhorst et al¹³ examined 819



Figure 5 Various changes in far-field (FF) and near-field (NF) electrograms between paired orthogonal bipoles in each point. In site A, the northeast (NE) bipolar pair demonstrates clear late potentials, which is not identified in the southeast (SE) bipolar pair. In site B, NE demonstrates a tiny but sharp near-field EGM, which is not identified in SE. In site C, SE describes the discrete near-field potential, which might be fused with the far-field EGMs in NE. In site D, both NE and SE identified the near-field potentials. However, the voltage was significantly greater in SE and the morphology changes dramatically.



Figure 6 Voltage variation between the higher and lower voltages in local ventricular abnormal activity sites (in both far- and near-field electrograms) assessed by using diagonally orthogonal bipolar pairs.

EGMs in 11 patients with prior infarction and VT during atrial and RV pacing; of these EGMs, 8% of EGMs showed ≤1.5 mV in atrial pacing and >1.5 mV in RV pacing and another 8% of EGMs showed >1.5 mV in atrial pacing and ≤1.5 mV in RV pacing. Our results are generally consistent with these findings while being analyzed in the same way (Supplemental Table 1). Recently, Tung et al examined the effect of the activation direction on the voltage map. They demonstrated the effect of different wavefronts on the voltage by pacing from different ventricular sites during substratebased VT ablation. Overlap of the scar area on the map between different wavefronts was analyzed. A different activation wavefront revealed 22% variation in a median bipolardefined scar area (<0.5 mV), and the concordance between wavefronts was lower in patients with mixed scar (0.5-1.5 mV) than in those with dense scar (<0.5 mV).

Instead of changing the activation direction by pacing from different sites, we examined the bipolar EGM variation between diagonally orthogonal bipolar pairs. With this method, we could compare the EGMs on the same beat, excluding spatial and temporal variations. In addition, we characterized the correlation with MRI-defined scar regions, demonstrating that the direction of bipolar pairs results in a mean of 30% variation from the higher to the lower voltage and that the variation was significantly greater in the MRIdefined border area. Local EGMs were associated with the electrode size, interelectrode spacing, activation vector, and the angle of bipolar orientation, contact, and filter.¹⁴ In the MRI-defined border and scar areas, propagation may vary more widely because of the heterogeneity between the fibrous tissue and interposed surviving myocardial fibers. In addition, there is a greater available mass of the normal far-field myocardium, contributing to the local bipolar EGMs in the border area adjacent to the healthy muscle, resulting in greater variability in the relationship of nearfield and far-field activation within the same field of view. The variation reached as much as 50% when the activation wavefront faced orthogonally to the one bipolar pair and parallel to the other. When the activation wavefront is parallel in

relation to the electrode pair, the bipolar spike will be of maximum amplitude, where, if it is orthogonal, both electrodes will record the same wavefront at the same time, resulting in the absence of the spike.¹⁵ However, the extent of the variation was not this great, indicating that this assessment was relatively gross. For a more precise interpretation of local bipolar EGMs, more detailed information on the endocardial and intramural activation is required. For example, the Purkinje network will carry the impulses to insertion points and depolarize the ventricular wall mainly from the endocardium to the epicardium. However, the HD-32 Grid catheter in this study was not able to analyze this 3D activation. As a next step, it would be more interesting to assess the EGMs in relation to the 3D activation with a higher resolution.

Effect of the bipolar direction on the detection of LAVA

Although several studies have reported the effect of the wavefront direction on voltage,^{7,13,15} there are a few reports on the effect of the wavefront on abnormal potentials.^{16,17} Brunckhorst et al¹⁶ compared the incidence of multipotential EGMs between atrial and RV pacing. They reported that 26.7%, 25.5%, and 47.8% of multipotential EGMs were detected only in atrial pacing, only in RV pacing, and in either of them, respectively. Multiple factors such as the angle between the activation direction and the bipolar electrode pair, the catheter design, and the definitions of multipotential EGM vs LAVA could explain this slight discrepancy. Also, changing the global activation by pacing from different sites may provide a different effect on EGMs as compared to changing only the bipolar direction.

Two main aspects should be considered on the detection and characteristics of LAVAs, namely, the catheter design and the tissue structure. As regards the catheter design, electrode size, interelectrode spacing, and bipolar electrode orientation are key factors. Whereas for the tissue structure, in relation to the catheter deployment, the orientation and size of the surviving and scar tissues as well as the activation of the neighboring healthy tissue and that of the surviving tissue may all be related in LAVAs.

With the diagonal bipolar pairs used in the present study, the electrode size was 1 mm with the surface area of 2.51 mm² and the interelectrode spacing was $3\sqrt{2}$ mm. Both larger electrode size and interelectrode spacing will generally fail to characterize the local tissue in detail.¹⁸ In addition to the difference in size of other existing multipolar mapping catheters (eg, PentaRay [3.14mm²], Biosense Webster Inc., Diamond Bar, CA; and Orion [0.4 mm²], Boston Scientific, Marlborough, MA), interelectrode spacing is larger with this configuration. A smaller spacing configuration of along vs across spline pairs would reduce the farfield effect and more accurately display the local activity. However, in the present study, we chose diagonal pairs, as this preserved the electrode spacing and the mapping point position between the pairs. Therefore, the difference in EGMs was a direct result of the orientation of the activation wavefront relative to the orientation of the bipolar pair; the grid design of this catheter specifically allowed us to explore this effect. In relation to the catheter design, both the activation direction of the neighboring normal tissue that creates far-field EGMs and the activation direction of the residual tissue in the fibrotic area that creates near-field EGMs affect the local EGMs; thus even when the same point was assessed, diagonally orthogonal bipolar pairs may show a discrepancy in abnormal potential distribution and the characteristics of abnormal potentials such as fractionation, splitting, or lateness of local potentials.

Although the present study was not able to demonstrate the role of these mismatched LAVA regions in VT as these EGMs were recorded in an animal model with or without VT, this finding is important for the concept of substratebased VT ablation. As VT substrate ablation, several strategies have been reported: scar dechanneling,¹⁹ late potentials ablation,²⁰ scar homogenization,²¹ core isolation,²² and LAVA elimination,^{12,23} which are all relying on the detection of low voltage areas and abnormal potentials.

Recent studies have reported better outcomes and advantages of multipolar catheters to detect LAVAs.^{6,24} Although a large number of points with a multipolar catheter may offset the effect of the wavefront direction on the local EGMs, many may simply be duplicated without adding any further information. Alternatively, automatic selection of the optimal or true EGM guided by the additional wavefront information may improve LAVA detection and voltage measurement. The real clinical effects of highdensity vs lower-density mapping points with the consideration of the wavefront direction should be examined in future studies.

Clinical implications

This study underscores the significance of the relationship between activation direction and bipolar pair direction with regard to the assessment of the local voltages. In addition, this relationship affects the detection of LAVAs. Although thousands of points with multiple point acquisitions at the same location with different catheter orientation may reduce this misassessment, this would require more time and generate more redundant data. A new technology using an assessment of the wavefront direction in the acquisition of 1 point may reduce acquisition time and data volume.

Study limitations

First, although mathematical algorithms would be desirable to ensure standardization and reproducibility, LAVA analysis was performed manually. Second, although a threshold of <0.5, 0.5–1.5, >1.5 mV was used for the discrimination of the dense scar area, low voltage area, and normal voltage area, this may not completely match the MRI-defined scar area, because this value was defined with different methodology without MRI information from the human data by using a different catheter with different electrode size and spacing. The discrepancies between MRI-defined scar and voltagedefined scar may affect the shifting of the voltage range dependent on the orthogonal bipolar recordings. Third, EGM recordings in the present study were made in different rhythms (including sinus rhythm and paced rhythm) and at different rates. However, the scope of the study was not to define the optimal voltage cutoff values for this catheter but to delineate the effect of the bipolar direction on voltage and LAVAs at individual sites, so this point may have not changed the result. Fourth, we did not compare low voltage areas, as done in the study by Tung et al. However, this is not a significant limitation of our study, because we focused on the effect on the EGMs with the different direction of bipolar pairs as individual points. Finally, contact force is known to affect the recorded EGMs but currently no multipolar mapping catheters are capable of contact force measurement.

Conclusion

A comparison of orthogonal bipolar pairs at individual sites in a sheep infarct model demonstrates the effect of bipolar orientation on local EGM voltage and LAVA detection. Voltage differs by $\sim 30\%$ between orthogonal bipolar pairs. Up to 30% of LAVA EGMs may be missed by looking at 1 bipolar direction only.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018. 07.020.

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1026 4-3. Impact of bipolar spacing and direction on the scar threshold

1027 **Background and purpose of the study**

1028 Following the prior 2 studies, we are interested in the effect of bipolar spacing and orientation on the optimal scar 1029 threshold to detect the infarcted region. As we have mentioned above, each company has developed a company-1030 specific multipolar mapping catheter. Although low-voltage threshold of <1.5 mV⁵⁵, and dense scar threshold of<0.5mV have been widely used for identifying a scar region in the left ventricle, the cut-off values, in fact, may be 1031 1032 different in each of them. In this study, we aim to elucidate the effect of an interelectrode spacing and bipolar 1033 orientations on the scar threshold, using the same catheter, system, and animal model as previous two studies. In 1034 particular, we explore the optimal threshold in two configurations of HD-grid catheters (Figure 1, HD-16 and HD-1035 32), and examine the impact of electrode spacing and bipolar direction on the scar-threshold.

1036 Methods

- 1037 Again, using the HD-grid catheter, not only unipolar EGMs but also bipolar EGMs were acquired during sinus rhythm
- 1038 from electrode pairs along to the catheter shaft (eg. A1-A2, A2-A3 etc for the HD-32-Grid, and A1-A3, A3-A5 etc
- 1039 for the HD-16-Grid), across to the catheter shaft (A1-B1, B1-C1 etc for both HD-32-Grid and HD-16-Grid), and
- 1040 diagonal directions (north-east [NE] and south-east [SE]; A1-B2, B1-A2 etc for the HD-32-Grid, and A1-B3, B1-A3
- 1041 etc for the HD-16-Grid). Scar was defined by the MRI images integrated on the 3D-EAM, and the optimal cut-off 1042 value of the local voltage and the predictive accuracy for scar identification was calculated based on the receiver 1043 operating characteristic (ROC) analysis. Finally, these values calculated from different bipolar configurations were 1044 compared each other.
- 1045

1046



1047 Figure 4-3. Bipolar configuration and EGMs from the HD-32 Grid catheter

1048 All electrodes were used for HD-32 Grid catheter (A). EGMs were collected from along (eg. A1-A2, A2-A3...D7-

1049 D8), across (eg. A1-B1, B1-C1, C1-D1, A2-B2, B2-C2...C8-D8), north-east diagonal (eg. A2-B1, B2-C1, C2-1050 D1...C8-D7), and south-east diagonal (eg. A1-B2, B1-C2, C1-D2...C7-D8) electrodes. Every other electrode on 1051 each spline is skipped to produce a HD-16 configuration, which is simulating the Advisor[™] HD Grid mapping 1052 catheter (Abbott, Minneapolis, MN, USA) (B). EGMs are collected from along (eg. A1-A3, A3-A5...D7-D8), across 1053 (eg. A1-B1, B1-C1, C1-D1, A3-B3, B3-C3...C7-D7), north-east diagonal (eg. A3-B1, B3-C1, C3-D1...C7-D5), and 1054 south-east diagonal (eg. A1-B3, B1-C3, C1-D3...C5-D7) electrodes. The MRI-image with MRI-defined scar is 1055 merged on the 3D mapping system. From one acquisition, 4 EGMs are collected from both HD-32 (A) and HD-16 1056 (B) configurations (B), allocated to MRI-defined scar and non-scar areas, and used for the analysis. Local voltages 1057 automatically calculated from peak-to-peak voltages consist in the combination of far- (yellow arrows) and near-field 1058 (red arrows) components. Note that far-filed components in HD-16 are larger than HD-32 (a,c,d). However, near-1059 field components are not always the case; larger in HD-32 (a,d) but smaller in HD-16 (c).

1060

1061 **Results**

1062 From 456 total acquisition sites (mean 76+/-12 per case), 14750 points with the HD-16 and 32286 points with the 1063 HD-32 configuration for bipolar EGMs were analyzed. For bipolar voltages, the optimal cut-off value to detect the 1064 MRI-defined scar based on the Youden's Index, and the area under the ROC curve (AUROC) differed depending on 1065 the spacing and orientation of bipoles as shown in Table 4-3-1; across 0.84mV (AUROC:0.920, 95%CI:0.911-0.928), 1066 along 0.76mV (AUROC:0.903, 95%CI:0.893-0.912), north-east direction (NE) 0.95mV (AUROC:0.923, 1067 95%CI:0.913-0.932), and south-east direction (SE), 0.87mV (AUROC:0.906, 95%CI:0.895-0.917) in HD-16; and 1068 across 0.83mV (AUROC:0.917, 95%CI:0.911-0.924), along 0.46mV (AUROC:0.890, 95%CI:0.883-0.897), NE 1069 0.89mV (AUROC:0.923, 95%CI:0.917-0.929), and SE 0.83mV (AUROC:0.913, 95%CI:0.906-0.920) in HD-32. 1070 Optimal cut-off values and AUROCs calculated from different bipolar configurations were compared in Table 4-3-1071 2. Significant differences in AUROC were seen between HD-16 along vs. across (P=0.002), HD-16 NE vs. SE 1072 (P=0.01), HD-32 NE vs. SE (P<0.0001), and HD-16 along vs. HD-32 along (P=0.006).

1073

1074

1075 Table 4-3-1. Optimal cut-off value based on all acquired points

| | Analyzed | Optimal Cutoff | | Sonsitivity % | Specificity % | Spearman Correlation |
|----------------------------|----------|----------------|---------------------|-----------------|-----------------|-------------------------|
| | Foints | voltage, mv | Aditoc (35 % ci) | Sensitivity, 70 | Specificity, 70 | correlation, p |
| HD16 | | | | | | |
| Unipolar | 5554 | 4.91 | 0.741 (0.728–0.755) | 84.3 | 61.2 | 0.410* |
| Across (3 mm) | 4219 | 0.84 | 0.920 (0.911–0.928) | 84.9 | 85.2 | 0.709* |
| Along (3 mm) | 4210 | 0.76 | 0.903 (0.893–0.912) | 81.8 | 83.2 | 0.686* |
| NE (4.23 mm) | 3123 | 0.95 | 0.923 (0.913–0.932) | 86.0 | 84.9 | 0.708* |
| SE (4.23 mm) | 3198 | 0.87 | 0.906 (0.895–0.917) | 78.6 | 88.2 | 0.688* |
| HD-32 | | | | | | |
| Unipolar | 10998 | 4.89 | 0.745 (0.739–0.754) | 83.7 | 62.1 | 0.414* |
| Across (3 mm) | 8327 | 0.83 | 0.917 (0.911–0.924) | 84.5 | 85.3 | 0.702* |
| Along (1 mm) | 9601 | 0.46 | 0.890 (0.883–0.897) | 81.2 | 81.3 | 0.660* |
| NE (3.16 mm) | 7171 | 0.89 | 0.923 (0.917–0.929) | 86.3 | 84.2 | 0.709* |
| SE (3.16 mm) | 7187 | 0.83 | 0.913 (0.906–0.920) | 82.2 | 86.6 | 0.695* |
| Independent of orientation | | | | | | |
| 3 mm | 12 537 | 0.80 | 0.912 (0.907–0.918) | 83.4 | 84.6 | 0.700* |
| 3.16 mm | 14358 | 0.85 | 0.918 (0.913–0.922) | 83.9 | 85.5 | 0.702* |
| 4.23 mm | 6321 | 0.90 | 0.913 (0.906–0.921) | 82.0 | 86.6 | 0.697* |

AUROC indicates area under the ROC curve; NE, north-east; and SE, south-east. *P<0.001

1076

1077 Table 4-3-2. Comparison of AUROC between bipolar configurations

| | 1070 |
|-----------------------------|----------|
| Comparison of AUROC | P-values |
| HD 16 | |
| Across (3mm) vs Along (3mm) | 0.003 |
| NE (4.23mm) vs SE (4.23mm) | 0.01 |
| HD32 | |
| Across (3mm) vs Along (1mm) | < 0.0001 |
| NE (3.16mm) vs SE (3.16mm) | 0.01 |
| Regardless of orientation | |
| 1mm vs 3mm spacing | < 0.0001 |
| 1mm vs 3.16mm spacing | < 0.0001 |
| 1mm vs 4.23mm spacing | < 0.0001 |
| 3mm vs 3.16mm spacing | 0.05 |
| 3mm vs 4.23mm spacing | 0.8 |
| 3.16mm vs 4.24mm spacing | 0.14 |
| | 1090 |

Summary and conclusion

As shown in the results and tables, the optimal cutoff value to discriminate scar from healthy tissue is specific to bipolar spacing and orientation, which may provide a difference in accuarcy.

Interestingly, smallest bipolar spacing (1 mm) less effectively discriminate scar from healthy tissue. This unexpected result may be explained by the fact that local voltages in the scar areas were more heterogeneous, with both far-field and near-field voltages measured from the electrodes with smaller

spacing. As previously demonstrated, far-field components increase more proportionally increase as the spacing

1092 increases, while near-field components are more sensitive to the local tissue and exaggerated in smaller electrode

spacing. As a result, far- and near-field voltages may be more frequently overlapped in EGMs acquired from

smaller spacing, while, probably in bipoles with larger spacing, local voltages were more uniformly measured from

1095 the larger far-field components in scar areas as described in a previous study.

- 1096 In conclusion, the threshold to discriminate scar (vs MRI) from healthy tissue should be specifically defined
- 1097 according to the bipolar configuration, but relatively high accuracy is preserved in any bipolar configuration with
- 1098 HD-grid when the specific cutoff is used for each bipolar configuration.
- 1099
- 1100 Manuscript is in publication; Circ Arrhythm Electrophysiol. 2019 Sep;12(9):e007158. doi:
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Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Impact of Spacing and Orientation on the Scar Threshold With a High-Density Grid Catheter

BACKGROUND: Multipolar catheters are increasingly used for highdensity mapping. However, the threshold to define scar areas has not been well described for each configuration. We sought to elucidate the impact of bipolar spacing and orientation on the optimal threshold to match magnetic resonance imaging-defined scar.

METHOD: The HD-Grid catheter uniquely allows for different spatially stable bipolar configurations to be tested. We analyzed the electrograms with settings of HD-16 (3 mm spacing in both along and across bipoles) and HD-32 (1 mm spacing in along bipoles and 3 mm spacing in across bipoles) and determined the optimal cutoff for scar detection in 6 infarcted sheep.

RESULTS: From 456 total acquisition sites (mean 76±12 per case), 14750 points with the HD-16 and 32286 points with the HD-32 configuration for bipolar electrograms were analyzed. For bipolar voltages, the optimal cutoff value to detect the magnetic resonance imaging-defined scar based on the Youden's Index, and the area under the receiver operating characteristic curve (AUROC) differed depending on the spacing and orientation of bipoles; across 0.84 mV (AUROC, 0.920; 95% CI, 0.911-0.928), along 0.76 mV (AUROC, 0.903; 95% CI, 0.893-0.912), north-east direction 0.95 mV (AUROC, 0.923; 95% CI, 0.913-0.932), and south-east direction, 0.87 mV (AUROC, 0.906; 95% CI, 0.895–0.917) in HD-16; and across 0.83 mV (AUROC, 0.917; 95% CI, 0.911-0.924), along 0.46 mV (AUROC, 0.890; 95% CI, 0.883-0.897), north-east direction 0.89 mV (AUROC, 0.923; 95% CI, 0.917-0.929), and south-east direction 0.83 mV (AUROC, 0.913; 95% CI, 0.906-0.920) in HD-32. Significant differences in AUROC were seen between HD-16 along versus across (P=0.002), HD-16 north-east direction versus south-east direction (P=0.01), HD-32 north-east direction versus south-east direction (P<0.0001), and HD-16 along versus HD-32 along (P=0.006). The AUROC was significantly larger (P<0.01) when only the best points on each given site were selected for analysis, compared with when all points were used.

CONCLUSIONS: Spacing and orientation of bipoles impacts the accuracy of scar detection. Optimal threshold specific to each bipolar configuration should be determined. Selecting one best voltage point among multiple points projected on the same surface is also critical on the Ensite-system to increase the accuracy of scar-mapping.

VISUAL OVERVIEW: A visual overview is available for this article.

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The full author list is available on page 10.

Key Words: arrhythmia electrophysiology = magnetic resonance spectroscopy = myocardial infarction = sheep = tachycardia ventricular

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WHAT IS KNOWN?

 Areas with the voltage between 0.5 and 1.5 mV have been defined as abnormal low voltage areas. However, these thresholds may be dependent on the electrode spacing and the angle between bipolar direction and activation direction.

WHAT THE STUDY ADDS?

- Optimal cutoff value to discriminate scar from healthy tissue is specific to bipolar spacing and orientation.
- Although scar areas are well discriminated from the healthy area in any bipolar configurations with the HD-grid catheter (Advisor) with both a sensitivity and specificity of 80% to 85%, smallest bipolar spacing (1 mm) showed relatively lower accuracy.
- Selecting the best point out of multiple points projected on the same given site may provide better accuracy to discriminate scar.

etection and characterization of myocardial scar is a prerequisite for substrate-based scar modification during sinus rhythm as mapping during ventricular tachycardia (VT) can be performed in only 30% to 40% of cases.^{1,2} Bipolar voltage mapping has been correlated with dense scar defined by histopathology and magnetic resonance imaging (MRI) and has been universally implemented in clinical practice, with a statistically derived low voltage threshold of <1.5 mV.^{3,4} However, not only electrode size and spacing,⁵⁻⁷ but also the activation wavefront relative to the catheter orientation, influence the local voltage.⁸⁻¹⁰

The purpose of this study was to explore the optimal threshold in 2 configurations of HD-grid catheters (Figure 1), and compare the impact of electrode spacing and bipolar direction on the scar-threshold. Additionally, we aimed to assess the feature of bestduplicated point installed in the EnSite Precision system, which automatically selects the highest voltage point among multiple points projected on the same surface point to create more accurate maps.

METHODS

The data, methods used in the analysis, and materials used to conduct the research will not be made available for purposes of reproducing the results or replicating the procedure.

Animal Model for Myocardial Infarction

Experimental protocols were conducted in compliance with the Guiding Principles in the Use and Care of Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996). The study was approved by the institutional animal use and care committee. Six female sheep (age 4.5 years, 55.4±7.3 kg) were sedated with an intramuscular injection of

ketamine hydrochloride (20 mg/kg), acepromazine (0.1 mg/ kg), and buprenorphine (20 ug/kg). After an intravenous injection of propofol (2 mg/kg), each sheep was intubated, and anesthesia was maintained with 2% to 3% isoflurane. Sheep were ventilated with a respirator (CARESTATION/Carescape GE, Chicago), using room air supplemented with oxygen. An intravenous catheter was placed in the internal jugular vein for infusion of drugs and fluids. Arterial blood gases were monitored periodically, and ventilator parameters were adjusted to maintain blood gases within physiological ranges. A sheep myocardial infarction model was created by an experienced invasive cardiologist using selective ethanol injection (1–2 cc) in the distal one-third of the left anterior descending artery.

MRI Myocardial Scar Segmentation

Late gadolinium-enhanced cardiac MRI was performed 2 to 3 months after the creation of myocardial infarction. Image processing was performed by 2 trained technicians using the MUSIC software (EQUIPEX MUSIC, Liryc, Universite' de Bordeaux/INRIA, Sophia Antipolis, France). Segmentation was performed as described previously.¹¹ Briefly, the cardiac chambers, ventricular epicardium, ascending aorta, and coronary sinus were segmented using semi-automatic methods.¹¹ Although adaptive histogram thresholding was applied to segment dense scar (threshold set at 50% maximum signal intensity) and gray zone (from 35%–50%)^{12–14} from left ventricular wall segmentation, these regions were all defined as scar areas in the present study.

Electrophysiological Study and Mapping With HD-32 Grid Catheter

An electrophysiological study for scar mapping was performed 1 to 3 days after the MRI examination in surviving post-infarct sheep, using the HD-32 Grid catheter (Abbott, Minneapolis, MN) and 3D-electroanatomical mapping system (EnSite Precision system, Research version, Abbott, Minneapolis, MN), with identical sedation, analgesia, intubation and ventilation protocols as previously. A quadripolar diagnostic catheter (Inquiry, Abbott, Minneapolis, MN) was placed in the right ventricle, inferior vena cava, and coronary sinus. A quadripolar positioned at the level of the inferior vena cava was used as the reference catheter for unipolar electrograms. The left ventricular was mapped during sinus rhythm with the HD-32 Grid catheter (3 mm inter-electrode spacing and 1 mm electrode size) via a retrograde aortic approach and trans-septal approach. Multiple bipolar configurations were created as described in the following paragraph. A steerable long sheath (Agilis, Abbott, Minneapolis, MN) was used if required. The internal and external projection setting was set at 5 mm with 5 mm interpolation. Fieldscaling was applied for all maps. On the point acquisition, contact with the left ventricular endocardial surface was confirmed by fluoroscopy and the proximity indicator on the EnSite Precision system.

For the registration, all segmentations of MRI imaging, including scar and healthy areas, were exported as meshes and loaded into the EnSite Precision system. The registration algorithm with the Ensite-NavX Fusion module allowed dynamic molding of the 3D-electroanatomical mapping

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Figure 1. Bipolar configuration from the HD-32 Grid catheter.

A, All electrodes were used for HD-32 Grid catheter. Electrocardiograms (EGMs) were collected from along (eg, A1-A2, A2-A3...D7-D8), across (eg, A1-B1, B1-C1, C1-D1, A2-B2, B2-C2...C8-D8), north-east diagonal (eg, A2-B1, B2-C1, C2-D1...C8-D7), and south-east diagonal (eg, A1-B2, B1-C2, C1-D2...C7-D8) electrodes.
 B, Every other electrode on each spline is skipped to produce a HD-16 configuration, which is simulating the Advisor HD-Grid mapping catheter (Abbott, Minneapolis, MN). EGMs are collected from along (eg, A1-A3, A3-A5...D7-D8), across (eg, A1-B1, B1-C1, C1-D1, A3-B3, B3-C3...C7-D7), north-east diagonal (eg, A3-B1, B3-C1, C3-D1...C7-D5), and south-east diagonal (eg, A1-B3, B1-C3, C1-D3...C5-D7) electrodes.

geometry onto the MRI surface.¹⁵ After primary registration, the registered model was refined using a second set of fiducial points, for example, left atrium, coronary sinus, aortic root, left ventricular apex, and mitral annulus, judiciously placed in a stepwise fashion to further align both surfaces at sites of local mismatch.

Bipolar Configurations and Electrogram Analysis

With the HD-32 Grid catheter, an electrode pair can be selected to create a bipolar electrogram. By skipping every other electrode, electrograms with a HD-16 Grid configuration, which is similar to that of the Advisor HD-Grid mapping catheter (Abbott, Minneapolis, MN), were also simulated in each acquired beat, as shown in Figure 1. Electrograms were classified as MRI-defined scar or nonscar areas and used for further analysis (Figure 2). Using the research version of EnSite Precision system, the absolute distance of each mapped point from the surface geometry was calculated. All points within 5 mm from the surface were included in the study. As well as unipolar electrograms, bipolar electrograms were acquired from electrode pairs along to the catheter shaft (eg, A1-A2, A2-A3 etc for the HD-32-Grid, and A1-A3, A3-A5 etc for the HD-16-Grid), across to the catheter shaft (A1-B1, B1-C1 etc for both HD-32-Grid and HD-16-Grid), and diagonal directions (north-east [NE] and south-east [SE]; A1-B2, B1-A2 etc for the HD-32-Grid, and A1-B3, B1-A3 etc for the HD-16-Grid). Electrograms acquired from a distorted catheter and those with noise or artifacts were excluded. Unipolar and bipolar electrograms were filtered from 2 to 100 Hz, and 30 to 300 Hz, respectively and local voltages were automatically analyzed from peak-to-peak voltages. The optimal cutoff value of the local voltage and the preon the receiver operating characteristic (ROC) analysis. The same analysis was then performed using only best duplicated points, one of the default settings of EnSite Precision system, in which the electrogram with the highest amplitude is selected as a local electrogram when multiple points are projected on the same surface to create the voltage map. The optimal cutoff value and predictive accuracy were compared with the values calculated using all points (<5 mm from the surface).

Statistical Analysis

For continuous variables, data are expressed as mean (±SD) when they follow a normal distribution; or as median (25th percentile-75th percentile) if they do not. As a result, the former was used to describe the area under the ROC curve (AUROC), and the latter was applied to describe the voltages. Spearman correlation coefficient was also calculated. For categorical variables, data are described as numbers and percentages. According to the skewness, χ^{2} analysis or Fisher's exact test were used for categorical variables, and an ANOVA analysis or Kruskal-Wallis test were used for continuous variables. P values <0.05 were considered statistically significant. To compare the diagnostic capability of each method, we performed a 2-sided Student t test on the mean±SD of each area under curve calculated, with the approximation of their normal distribution. The optimal cutoff value to detect the MRI-defined scar was based on the Youden's Index

RESULTS

Electrogram Acquisition

The optimal cutoff value of the local voltage and the predictive accuracy for scar identification was calculated based from a total of 456 acquisition sites (mean 76±12 per

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The magnetic resonance imaging (MRI)-image with MRI-defined scar is merged on the 3D mapping system. From one acquisition, 4 EGMs are collected from both HD-32 (**A**) and HD-16 (**B**), allocated to MRI-defined scar and nonscar areas, and used for the analysis. Local voltages automatically calculated from peak-to-peak voltages consist in the combination of far- (yellow arrows) and near-field (red arrows) components. Note that far-field components in HD-16 are larger than HD-32 (a, c, d). However, near-field components are not always the case; larger in HD-32 (a, d) but smaller in HD-16 (c).

case) in prepared 6 infarcted sheep as shown in Table 1. Mapped points >5 mm further from the surface geometry or those with noise or artifact were excluded from the analysis. Five thousand five hundred fifty-four points with the HD-16 configuration and 10998 points with the HD-32 configuration for unipolar electrograms, and 14750 points with the HD-16 configuration and 32 286 points with the HD-32 configuration for bipolar electrograms were analyzed.

Unipolar Voltages

As unipolar voltages, 3337 points in healthy areas and 2217 points in scar areas with the HD-16 configuration, and 6687 points in healthy areas and 4311 points in scar areas with the HD-32 were analyzed (Table 2). There were no differences in unipolar voltage between HD-16 and HD-32 configurations in either healthy or scar areas (P=N.S.).

| Table 1. Baseline C | Characteristics (N=6) |
|---------------------|-----------------------|
|---------------------|-----------------------|

| Sheep No. | Sex | Age, y | Weight, kg | Total Acquisitions |
|-----------|-----|--------|------------|--------------------|
| 1 | f | 5 | 60 | 95 |
| 2 | f | 5 | 56.5 | 81 |
| 3 | f | 5 | 60 | 75 |
| 4 | f | 5 | 48 | 61 |
| 5 | f | 5 | 63 | 77 |
| 6 | f | 2 | 45 | 67 |

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| | No. of Points | Unipolar Voltage, mV |
|---------|---------------|----------------------|
| Healthy | | |
| HD-16 | 3337 | 5.62 [4.13-7.07] |
| HD-32 | 6687 | 5.63 [4.15-7.11] |
| Scar | | |
| HD-16 | 2217 | 3.98 [3.12-4.56] |
| HD-32 | 4311 | 3.99 [3.12-4.56] |

Bipolar Voltages

As bipolar voltages, 8950 points in healthy areas and 5800 points in scar areas with the HD-16 configuration, and 19882 points in healthy areas and 12 415 points in scar areas with the HD-32 configuration were analyzed. Median voltages in different configurations are given in Table 3 for the HD-16 configuration and in Table 4 for the HD-32 configuration.

Effect of Electrode Spacing and Orientation

The direct effect of electrode spacing independent of direction is reflected by the difference in median voltage between the HD-32 along (1 mm spacing) and HD-16 along bipolar electrograms (3 mm spacing) Table 5. Median voltages were significantly larger with 3 mm spacing in both healthy and scar areas (P<0.0001).

The direct effect of electrode direction independent of spacing is reflected by the difference in median voltage between along versus across bipolar electrograms in the HD-16, and NE versus SE bipolar electrograms in HD-16 and HD-32 configurations. In the scar areas, although the impact of bipolar orientation was not significant in 3 mm electrode spacing, it became significant when the inter-electrode spacing became larger

| Table 3. Bipolar Voltages With HD-16 Grid in Healthy and Scar A | Area |
|---|------|
|---|------|

| Bipolar Configuration (Inter- Electrode Spacing) | No. of points | Bipolar Voltage, mV |
|--|---------------|---------------------|
| Healthy | 8950 | |
| Across (3 mm) | 2584 | 1.89 [1.13-3.00] |
| Along (3 mm) | 2483 | 1.74 [1.00-2.87] |
| NE (4.23 mm) | 1958 | 2.16 [1.28-3.34] |
| SE (4.23 mm) | 1925 | 2.09 [1.31-3.24] |
| Scar | 5800 | |
| Across (3 mm) | 1635 | 0.35 [0.23-0.60] |
| Along (3 mm) | 1727 | 0.34 [0.21-0.60] |
| NE (4.23 mm) | 1165 | 0.41 [0.27-0.64] |
| SE (4.23 mm) | 1273 | 0.49 [0.33-0.79] |

NE indicates north-east; and SE, south-east.

| Table 4 | Binolas Voltagos | Mith UD 2 | Crid in H | a althu and | Cene Arene |
|----------|------------------|-------------|-----------|-------------|------------|
| laple 4. | bipolar voltages | VVIUI HD-54 | Grid in H | eartiny and | Scar Areas |

| Bipolar Configuration (Inter- Electrode Spacing) | No. of Points | Bipolar Voltage, mV |
|--|---------------|---------------------|
| Healthy | 19882 | |
| Across (3 mm) | 5151 | 1.88 [1.11-3.03] |
| Along (1 mm) | 5805 | 1.18 [0.57-2.14] |
| NE (3.16 mm) | 4492 | 2.00 [1.15-3.19] |
| SE (3.16 mm) | 4434 | 1.94 [1.16–3.13] |
| Scar | 12415 | |
| Across (3 mm) | 3176 | 0.35 [0.23-0.61] |
| Along (1 mm) | 3796 | 0.19 [0.12-0.37] |
| NE (3.16 mm) | 2679 | 0.36 [0.24-0.59] |
| SE (3.16 mm) | 2764 | 0.40 [0.27-0.68] |

NE indicates north-east; and SE, south-east.

and reached a 20% difference when the inter-electrode spacing was 4.23 mm, as shown in Table 5.

Optimal Cutoff Values

Optimal cutoff values to discriminate scar from healthy areas were determined using ROC analysis and are described in Tables 6 through 8. For unipolar HD16 electrograms, a cutoff voltage value of 4.91 mV was found (sensitivity 84.3%, specificity 61.2%), which did not change even when analyzed points were increased using points acquired with the HD-32 configuration (Table 6). These 2 configurations showed generally weaker spearman correlation (ρ <0.5) compared with bipolar configurations. For bipolar voltages, the optimal cutoff voltage value and the AUROC differed depending on spacing and the orientation of bipoles; across 0.84 mV (AUROC, 0.920; 95% CI, 0.911-0.928), along 0.76 mV (AUROC, 0.903; 95% CI, 0.893-0.912), NE 0.95 mV (AUROC, 0.923; 95% CI, 0.913-0.932), and SE 0.87 mV (AUROC, 0.906; 95% CI, 0.895-0.917) in HD-16; and across 0.83 mV (AUROC, 0.917; 95% CI, 0.911-0.924), along 0.46 mV (AUROC, 0.890; 95% CI, 0.883-0.897), NE 0.89 mV (AUROC, 0.923; 95% CI, 0.917-0.924), and SE 0.83 mV (AUROC, 0.913; 95% CI, 0.906-0.920) in HD-32. When we focused on the spacing, the optimal cutoff voltage values and AUROCs were as follows: 1 mm spacing 0.46 mV (AUROC, 0.890; 95% CI, 0.883-0.897), 3 mm spacing 0.80 mV (AUROC, 0.912; 95% CI, 0.907-0.918), 3.16 mm spacing 0.89 mV (AUROC, 0.918; 95% CI, 0.913-0.922) and 4.23 mm spacing 0.90 mV (AUROC, 0.913; 95% CI, 0.906-0.921). A strong spearman correlation $(\rho \ge 0.7)$ was obtained regardless of bipolar configurations. Although relatively high accuracy and reliability was preserved in all bipolar configurations, significant differences were observed between settings as shown in Table in the Data Supplement.

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| | Voltage in Healthy Areas, mV | P Values | Voltage in Scar Areas, mV | P Values |
|---|--------------------------------------|----------|--------------------------------------|----------|
| Comparison of spacing | ·^ · | | | |
| HD-16 along vs. HD-32 along (3 mm vs. 1 mm spacing) | 1.74 [1.00–2.87] vs 1.18 [0.57–2.14] | <0.0001 | 0.34 [0.21–0.60] vs 0.19 [0.12–0.37] | <0.0001 |
| Comparison of orientation | | | | |
| HD-16 across vs HD-16 along (3 mm spacing) | 1.89 [1.13–3.00] vs 1.74 [1.00–2.87] | 0.002 | 0.35 [0.23–0.60] vs 0.34 [0.21–0.60] | 0.2 |
| HD-32 NE vs HD-32 SE (3.16 mm spacing) | 2.00 [1.15–3.19] vs 1.94 [1.16–3.13] | 0.35 | 0.36 [0.24–0.59] vs 0.40 [0.27–0.68] | <0.0001 |
| HD-16 NE vs HD-16 SE 2.16 [1.28–3.34] vs 2.09 [1.31–3.24] | | 0.76 | 0.41 [0.27–0.64] vs 0.49 [0.33–0.79] | <0.0001 |

NE indicates north-east; and SE, south-east.

Specifically, the HD-32 along configuration (1 mm spacing) showed significantly higher AUROC values than in the HD-32 across configuration (3 mm spacing; P=0.001), and the HD-16 along (3 mm spacing; P=0.006). Additionally, significant difference in AUROC was observed between 1 mm spacing versus 3 mm, 3.16 mm and 4.23 mm spacing (P<0.001); HD-32 along configuration (1 mm spacing) demonstrated a weaker spearman correlation, showing a lower reliability.

All Points Versus Selected Points Among Multiple Duplicated Points

When only selected points (those with the largest voltage) were used instead of all points for analysis, the optimal cutoff unipolar values for HD-16 and HD-32 were 4.85 mV and 5.01 mV, respectively (Table 7). For bipolar volt-

Table 6. Optimal Cutoff Value Based on All Acquired Points

ages, the optimal cutoff voltage value differed depending on spacing and the orientation of the bipoles as follows: across 0.99 mV, along 1.01 mV, NE 1.17 mV, and SE 1.16 mV in HD-16; and across 0.90 mV, along 0.84 mV, NE 1.18 mV, and SE 1.02 mV in HD-32. Both the AUROC and Spearman correlation were generally significantly larger when only the best points on each given site were selected for analysis compared with when all points were used for analysis, as shown in Table 8.

DISCUSSION

Major Findings

In the present study, we examine the impact of bipolar spacing and orientation on the scar threshold and demonstrate the following.

| | Analyzed Points | Optimal Cutoff Voltage, mV | AUROC (95% CI) | Sensitivity, % | Specificity, % | Spearman Correlation, ρ |
|-------------------------|--------------------|-------------------------------|---------------------|----------------|----------------|----------------------------|
| HD16 | | | | | | |
| Unipolar | 5554 | 4.91 | 0.741 (0.728–0.755) | 84.3 | 61.2 | 0.410* |
| Across (3 mm) | 4219 | 0.84 | 0.920 (0.911–0.928) | 84.9 | 85.2 | 0.709* |
| Along (3 mm) | 4210 | 0.76 | 0.903 (0.893–0.912) | 81.8 | 83.2 | 0.686* |
| NE (4.23 mm) | 3123 | 0.95 | 0.923 (0.913–0.932) | 86.0 | 84.9 | 0.708* |
| SE (4.23 mm) | 3198 | 0.87 | 0.906 (0.895–0.917) | 78.6 | 88.2 | 0.688* |
| HD-32 | | | | | | |
| Unipolar | 10998 | 4.89 | 0.745 (0.739–0.754) | 83.7 | 62.1 | 0.414* |
| Across (3 mm) | 8327 | 0.83 | 0.917 (0.911–0.924) | 84.5 | 85.3 | 0.702* |
| Along (1 mm) | 9601 | 0.46 | 0.890 (0.883–0.897) | 81.2 | 81.3 | 0.660* |
| NE (3.16 mm) | 7171 | 0.89 | 0.923 (0.917–0.929) | 86.3 | 84.2 | 0.709* |
| SE (3.16 mm) | 7187 | 0.83 | 0.913 (0.906–0.920) | 82.2 | 86.6 | 0.695* |
| Independent of orientat | tion | | | | | |
| 3 mm | 12 537 | 0.80 | 0.912 (0.907–0.918) | 83.4 | 84.6 | 0.700* |
| 3.16 mm | 14358 | 0.85 | 0.918 (0.913–0.922) | 83.9 | 85.5 | 0.702* |
| 4.23 mm | 6321 | 0.90 | 0.913 (0.906–0.921) | 82.0 | 86.6 | 0.697* |

AUROC indicates area under the ROC curve; NE, north-east; and SE, south-east. *P<0.001

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| | Analyzed Points | Optimal Cutoff Voltage, mV | AUROC (95% CI) | Sensitivity, % | Specificity, % | Spearman Correlation, p |
|--------------------|--------------------|-------------------------------|---------------------|----------------|----------------|----------------------------|
| HD16 | | | | | | |
| Unipolar | 3930 | 4.85 | 0.791 (0.777–0.806) | 88.4 | 65.3 | 0.494* |
| Across (3 mm) | 695 | 0.99 | 0.931 (0.911–0.951) | 83.8 | 88.7 | 0.674* |
| Along (3 mm) | 1028 | 1.01 | 0.946 (0.932-0.960) | 90.4 | 86.1 | 0.723* |
| NE (4.23 mm) | 771 | 1.17 | 0.955 (0.940–0.970) | 89.9 | 89.5 | 0.750* |
| SE (4.23 mm) | 761 | 1.16 | 0.938 (0.921–0.955) | 87.7 | 86.8 | 0.748* |
| HD-32 | | | | | | |
| Unipolar | 5284 | 5.01 | 0.823 (0.811–0.834) | 89.5 | 70.1 | 0.553* |
| Across (3 mm) | 840 | 0.90 | 0.943 (0.927–0.958) | 82.9 | 92.7 | 0.716* |
| Along (1 mm) | 1167 | 0.84 | 0.909 (0.892–0.926) | 84.8 | 80.8 | 0.658* |
| NE (3.16 mm) | 1071 | 1.18 | 0.963 (0.953–0.974) | 94.5 | 88.6 | 0.759* |
| SE (3.16 mm) | 1101 | 1.02 | 0.928 (0.912–0.943) | 87.7 | 86.8 | 0.718* |
| Independent of ori | entation | | | | | |
| 3 mm | 1868 | 1.01 | 0.944 (0.933–0.955) | 87.7 | 87.6 | 0.707* |
| 3.16 mm | 2171 | 1.06 | 0.946 (0.937–0.956) | 90.9 | 87.4 | 0.741* |
| 4.23 mm | 1532 | 1.16 | 0.947 (0.935-0.958) | 88.3 | 88.4 | 0.751* |

AUROC indicates area under the ROC curve; NE, north-east; and SE, south-east. *P<0.001.

Using high-density mapping:

- Bipolar voltage increases as the inter-electrode spacing increases in both healthy and scar tissue.
- 2. In scar areas, bipolar orientation may impact the voltage, particularly when the bipolar spacing is larger.
- Optimal cutoff value to discriminate scar from healthy tissue is specific to bipolar spacing and orientation.
- Smallest bipolar spacing (1 mm) less effectively discriminate scar from healthy tissue.
- Selecting the best point out of multiple points projected on the same given site may provide better accuracy to discriminate scar.

The Impact of the Bipolar Spacing on the Local Voltage and Scar Threshold

Our results demonstrate that bipolar voltages generally increase as the inter-electrode spacing increases in both healthy and scar areas. Excluding the effect of wavefront direction by comparing HD-16 along (3 mm spacing) versus HD-32 along (1 mm spacing), resulted in a remarkable difference. Although each bipolar configuration provided high sensitivity and specificity of ≈80% to 85% in discriminating scar from healthy tissue, with an optimal cutoff value for each bipolar setting, the smallest spacing (1 mm) seemed to be less accurate. This unexpected result may be explained by the fact that local voltages in the scar areas were more heterogeneous, with both far-field and near-field voltages measured from the electrodes with smaller spacing. As previously demonstrated, far-field components increases more proportionally increase as the spacing increases, while near-field components are more sensitive to the local tissue and exaggerated in smaller electrode spacing.⁷ As a result, far- and near-field voltages may be more frequently overlapped with smaller spacing, while, probably in bipoles with larger spacing, local

| Table 8. | Comparison of the Al | JROC Between All-Point Analysis Versus | |
|----------|----------------------|--|---|
| Selected | Point Analysis | | |
| 1 | | | ì |

| | All Points (Larg | | P Values |
|------------------------|------------------|-------------|----------|
| HD16 | | | |
| Unipolar | 0.741±0.007 | 0.791±0.007 | <0.001 |
| Across (3 mm) | 0.920±0.004 | 0.931±0.100 | 0.31 |
| Along (3 mm) | 0.903±0.005 | 0.946±0.007 | <0.001 |
| NE (4.23 mm) | 0.923±0.005 | 0.955±0.007 | 0.003 |
| SE (4.23 mm) | 0.906±0.006 | 0.938±0.009 | 0.004 |
| HD-32 | | | |
| Unipolar | 0.745±0.005 | 0.823±0.006 | <0.001 |
| Across (3 mm) | 0.917±0.003 | 0.943±0.008 | 0.004 |
| Along (1 mm) | 0.890±0.003 | 0.909±0.009 | 0.01 |
| NE (3.16 mm) | 0.923±0.003 | 0.963±0.005 | <0.001 |
| SE (3.16 mm) | 0.913±0.004 | 0.928±0.008 | 0.065 |
| Independent of orienta | ation | | |
| 3 mm spacing | 0.912±0.003 | 0.944±0.005 | <0.001 |
| 3.16 mm spacing | 0.918±0.002 | 0.946±0.005 | <0.001 |
| 4.23 mm spacing | 0.913±0.004 | 0.947±0.006 | <0.001 |

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voltages were more uniformly measured from the larger far-field components in scar areas as described in a previous study.¹⁶

The effect of spacing on the optimal cutoff values has been elegantly described by Tung et al.¹⁷ They demonstrate an increasing linear relationship between optimal voltage thresholds for scar and wider bipolar spacing. In their study, the optimal cutoff value with a duo-decapolar catheter (1 mm electrode length and 2 mm spacing) was 6.7 mV for unipolar, and 2.02 mV for bipolar configurations. Interestingly, optimal cutoff values of both unipolar- and bipolar-voltages with the HD-16 configuration were 4.91 mV and 0.76to 0.84 mV in the present study, much smaller than in Tung's report, even though the electrode length was the same (1 mm) and the HD-16 inter-electrode spacing was larger. One reason for this discrepancy may originate from the difference of the electrode surface area, as this is ≈3×larger in the duo-decapolar catheter, impacting the voltage threshold due to a larger far-field effect. This may also suggest a larger contribution from far-field signal component with larger surface electrodes. Regarding inter-electrode spacing, the commercially available HD-grid catheter (Advisor) may provide a larger voltage (with a greater far-field effect) than other commercially available multipolar mapping catheters due to a larger inter-electrode spacing. However, other factors affecting electrograms, such as electrode size and surface area should be acknowledged.

Interestingly, as theoretically expected, the present study demonstrated that the optimal cutoff value for unipolar voltage was similar between HD-16 and HD-32, because the electrode size was the same between these 2 configurations even though a larger number of points was collected for the HD-32.

The Impact of the Orientation of Bipolar Pair on the Local Voltage and Scar Threshold

The angle between the bipolar orientation and activation front has been reported to affect local voltages.8-10 In scar areas, propagation may vary even more widely, due to the heterogeneity between fibrous tissue and interposed surviving myocardial fibers. In addition, a greater available mass of normal far-field myocardium contributes to the local bipolar electrograms in the border area adjacent to the healthy muscle, resulting in a combination of near-field and far-field electrograms. Peak-to-peak voltages in these areas showed ≈30% to 35% variation between orthogonally diagonal bipolar pairs at the same location.9 Although this effect may have been nullified by adding mapping data from other catheter orientations, we still observed that the impact of bipole orientation in scar areas was exaggerated when the bipolar spacing was larger, as shown in

Table 5. As far-field components are usually exaggerated with larger inter-electrode spacing,⁷ this finding may be linked to the relation between far-field voltage versus activation direction in scar areas. Since the present study did not show a significant difference between orthogonal bipolar directions for the 3 mm spacing, a smaller inter-electrode spacing may offset the impact of this far-field effect associated with overall activation direction. However, this should be confirmed by using bipoles with much smaller spacing. Additionally, the clinical impact of the limited difference ($\approx 20\%$) should be examined in clinical studies using an ablation strategy based on these different cutoff values.

The Impact of Selecting the Best Points in the Projected Location

The present study demonstrated that the optimal cutoff values calculated from selected points on each projected site provided a higher accuracy for scar discrimination compared with those calculated from all acquired points. Although high-density mapping with a multipolar mapping catheter can display substrate with higher spatial resolution, multiple points may be deleterious as they may not provide the true voltage at each given site due to orientation of bipoles versus activation direction.

However, one possible important limitation to this function is that by selecting the highest amplitude signal, it may favor far-field components over the near-field ones, and therefore reduce the ability to display the local abnormal ventricular activities in the scar⁷ (Figure 3), and this limitation is critical for the recent approaches of VT substrate ablation.¹⁸⁻²² Additionally, the gap on the linear lesion may be missed by a voltage map when double potentials with large far-field components are identified along the linear lesion.

Scar Threshold in Commercially Used Catheter

The findings of the present study suggest that in the EnSite Precision system with the Advisor HD-Grid Mapping Catheter using the best points option, the threshold of 4.85 mV in unipolar voltage and 1.01 mV in bipolar voltage (3 mm along bipoles) may be used for scar detection. However, the value derived from the animal data maybe not always applicable to the human data.

Recently, industry has provided several types of multipolar mapping catheters with different electrode size and inter-electrode spacing. Compared with the Advisor (3 mm inter-electrode spacing, 1 mm electrode length, surface area of 2.51 mm²), the PentaRay (Biosense-Webster Inc, Diamond Bar, CA) has a smaller inter-electrode spacing (2 mm) and similar electrode length (1 mm) but larger surface area (3.14 mm²). The

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Figure 3. Examples of best electrocardiograms (EGMs) selected out of multiple EGMs projected on a given site. In the scar border area, 4 duplicated points (A–D) are projected on the same surface point, (A) with the highest amplitude selected as the local voltage to create the voltage map. Although, EGMs at (B–D) depict local abnormal ventricular activities, this is not reflected on the map. Catheter is placed on a similar region but with a different acquisition and with a different acquisition and with a different angle. These adjacent points are projected on the same surface, and one of them with a highest voltage is picked up as a local voltage with a default setting of the commercial version of the NavX precision system, which results in missing a local abnormal EGMs. This situation more frequently happens on the scar border areas.

Orion (Boston Scientific, Marlborough, MA) has a smaller inter-electrode spacing (2.5 mm) and much smaller electrode size (0.4 mm²). Although bipolar voltages and local resolution are affected not only by the inter-electrode spacing, but also the electrode size (and not just electrode length), a direct comparison may be required to decide on superiority between these catheters. However, at the least, a threshold for scar detection should be set for each catheter. Since the commercially used HD-16 (Advisor) has a relatively large inter-electrode spacing, the resolution may be worse than for other multipolar mapping catheters. However, using multiple bipolar configurations may increase the resolution, and the detection of abnormal potentials such as local abnormal ventricular activities may be improved, and the sequential arrangement of electrodes may allow us to easily observe activation direction. However, this should be analyzed in a further study.

One Voltage Threshold or 2 Voltage Thresholds

Although we have been using 2 cutoff values for scar determination, this may not always be relevant to the clinical ablation strategy. First, although several strategies for VT substrate modification have been reported with good results, ¹⁸⁻²² distinguishing the so-called dense scar (<0.5 mV) from border area (0.5–1.5 mV) does not

help identifying critical electrograms/isthmuses as they can be found in both. This means that identification of the entire scar area may be more important than discrimination of dense scar.

Second, a value of <0.5 mV as dense scar has been previously determined through intraoperative mapping using an ablation catheter in patients with postinfarction VT.²³ Additionally, a value of ≥1.5 mV as healthy tissue is based on voltage mapping from the normal heart in the absence of structural disease, and the voltage between 0.5 mV and 1.5 mV defined as abnormal low voltage areas.⁴ However, dense scar does not mean the absence of residual myocyte bundles in these areas. The residual tissue inside scar generally provides low voltage and high-frequency electrograms represented by local near-field electrograms,²² which may be critical to VT circuits. However, mapping system will automatically consider the voltage of the largest electrogram, which most often is not the critical one, being the far-field component.¹⁶ Since there are huge overlaps of voltage values between residual surviving tissue and far-field electrograms from healthy tissue in the dense scar area (<0.5 mV), identifying truly dead scar may not be simple or feasible. Smaller electrodes with smaller inter-electrode spacing minimize the far-field effect and probably more frequently collect near-field components, but still not able to avoid overlap.7,16

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Clinical Implications

Larger inter-electrode spacing providing larger bipolar voltage values in both healthy and scar areas. Bipolar orientation affects local voltage and may not be completely set off by catheter manipulation, which certainly highlights the interest of omnipolar mapping.²⁴

Although voltage thresholds for scar detection are specific to the electrode configuration, the accuracy of discriminating scars from healthy tissue is generally high with high-density mapping using the HD-grid as described by the AUROC=0.9. Smaller spacing (1 mm) does not better discriminate scar areas from healthy areas than larger spacing, but may be superior in identifying local signal from surviving bundles in the scar. Finally, voltage detection of scar is improved by using the best voltage points. However, we have to emphasize that our results do not mean that smaller spacing is inferior to larger spacing in investigating critical electrograms for VT-substrate such as local abnormal ventricular activities. Local abnormal ventricular activities detection has been shown to be superior with smaller inter-electrode spacing⁷ and multiple bipolar orientations.^{9,24}

LIMITATIONS

First, the small number of animals is a significant limitation in this study. Additionally, this animal model is likely different from that seen in patients with postmyocardial infarction. The infarct produced in sheep is more homogeneous, with smaller border zone, for example. Therefore, the applicability of the cutoff values in the present study must be cautiously examined in human studies. However, it is useful to describe the impact of spacing and orientation on scar characterization, and that the accuracy is relatively highly preserved in high-density mapping with the HD-grid catheter when specific cutoff values are used. It is also important to acknowledge that the local electrogram amplitude is measured based on the peak-to-peak voltage which is automatically calculated by the system, that is, from mixed electrograms with far- and near-field components, especially in scar areas. It would have been interesting to have performed the study using different pacing vectors, which may form the basis for a further study. Finally, smaller inter-electrode spacing (1 mm along/1 mm across) may offset the effect of bipole orientation versus activation, but a catheter with such a design was not available.

CONCLUSIONS

Voltages in both scar and healthy areas are affected by the spacing and orientation of the bipolar electrode configuration. The threshold to discriminate scar (vs MRI) from healthy tissue should be specifically defined according to the bipolar configuration, but relatively high accuracy is preserved in any bipolar configuration with HD-grid when the specific cutoff is used for each bipolar configuration. Automatically selecting the best point out of multiple points projected on the same given site may reduce redundant data and increase accuracy. Including bipolar orientation in mapping systems should be considered in the future.

ARTICLE INFORMATION

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Circ Arrhythm Electrophysiol. 2019;12:e007158. DOI: 10.1161/CIRCEP.119.007158

1120 **4-4. Impact of electrode size on the local EGMs.**

1121 Background and purpose of the study

- 1122 We have demonstrated that local EGMs are strongly influenced by inter-electrode spacing and the angle between
- 1123 bipolar orientation and activation direction. Additionally, the scar threshold and the identification of LAVAs are also
- 1124 significantly affected by these settings.
- 1125 In this study, we focus on the effect of electrode size on local EGMs and elucidate the best configuration to collect
- 1126 near-field EGMs, reducing the far-field effect.

1127 Methods

- 1128 Six female sheep were used for this study. With a standard median sternotomy, the chest was opened and the heart
- 1129 was epicardially mapped with dedicated catheters prepared for this study. Two parallel regions were created on the
- 1130 left atrial appendage (LAA) and right ventricle (RV) by RF energy, and EGMs were collected from regions including
- 1131 healthy tissues, fat tissues, and scars and gaps as shown in **Figure 4-4-1**, using dedicated catheters; three unipolar
- 1132 catheters with different mini-electrode size (0.1mm, 0.2mm, and 0.5mm) with 3mm inter-electrode spacing were
- 1133 used. Additionally, one bipolar platform with micro-spacing (0.1mm) inter-electrode spacing was used as references
- 1134 (Figure 4-4-2). The effect of electrode size on unipolar and bipolar EGMs were assessed. The voltage ratio of non-
- 1135 fat to fat tissue (N/F-ratio) was calculated from the averaged voltages of non-fat tissue divided by each local voltage
- 1136 on the fat area. Gap/scar voltage ratio (G/S-ratio) was calculated from the voltage on the gap divided by the scar
- 1137 beside. N/F-ratio and G/S ratio was used as the index of a sensitivity to near-field EGMs. Larger N/F-ratio and G/S-
- 1138 ratio indicated a higher sensitivity to near-field EGMs and a reduced effect from far-field EGMs. G/S-ratio indicated
- 1139 sensitivity for gap detection.



Normal tissue

LAA

LA

RAA

RV

| | | A | |
|---|-------|---|---|
| P | | - | 2 |
| | - der | 0 | |

Fat tissue

RA

RV



LAA scar and gap



RV scar and gap

1140

- 1141 Figure 4-4-1. EGM collection with direct catheter contact
- 1142

UnipolesBipolesImage: Desting the series of the series of

1143

1144Figure 4-4-2. Dedicated catheters

1145

1146 **Results**

Unipolar- and bipolar-EGMs were collected from 3 sheep. In each sheep, EGMs were taken from 24 sites (24 unipolar EGMs and 12 bipolar EGMs) in each of the right atrium (RA), left atrium (LA), LAA, RV, RA with fat and RV with fat. Additionally, EGMs were collected from 12 sites (12 unipolar EGMs and 6 bipolar EGMs) both at the gap and on the scars created in the LAA and RV.

1151 Electrode size vs. unipolar EGMs

1152 Comparison between the three dedicated catheters and the PR, with the bipolar catheter with micro-spacing as a 1153 reference, is shown in Table 4-4. Unipolar EGM voltage, as shown in the Table 4-4-1, increased from 6.34 [4.06-1154 8.90]mV with a 0.1mm-electrode to 7.81 [5.63-10.50]mV with a 0.5mm-electrode in a healthy area, from 3.15 [1.77-1155 4.88] with a 0.1mm-electrode to 4.92 [2.26-6.35]mV with a 0.5mm-electrode in an area of fat, and from 2.5 [1.00-1156 4.3] with a 0.1mm-electrode to 3.59 [2.34-4.79]mv with a 0.5mm-electrode in a scar area. Unipolar EGM duration, 1157 as shown in the Table 4-4-2, increased from 34 [30-40]ms with a 0.1mm-electrode to 49 [42-51]ms with a 0.5mm-1158 electrode in a healthy area, from 49.5 [41.3-53]ms with a 0.1mm-electrode to 56 [51-63]ms with a 0.5mm-electrode 1159 in an area of fat, and from 43 [40-48]ms with a 0.1mm-electrode to 51 [50-54]ms with a 0.5mm-electrode in a scar 1160 area. Although both unipolar voltages and duration showed a tendency to increase in any tissue when the mini-1161 electrode size was larger, a particularly large difference in voltage was identified between the 0.2mm-electrode and 1162 the 0.1mm-electrode, and in duration between the 0.3mm-electrode and the 0.5mm-electrode.

1163

1164 Electrode size vs. bipolar EGMs

Bipolar EGM voltage, as shown in the **Table 4-4-3**, increased from 3.60 [2.37-4.74]mV with a 0.1mm electrode to 4.24 [3.42-5.78]mV with a 0.5mm electrode in a healthy area, from 0.87 [0.35-1.23]mV with a 0.1mm electrode to 1.05[0.54-1.81]mV with a 0.5mm electrode in an area of fate, and from 0.54 [0.38-0.72]mV with a 0.1mm electrode to 0.63[0.37-0.82]mv with a 0.5mm electrode in a scar area.

- Bipolar EGM duration, as shown in the Table 4-4-4, increased from 26 [23-33]ms with a 0.1mm electrode to 31 [25-
- 1170 37] ms with a 0.5mm electrode in a healthy area, from 35.5 [29-43.8]ms with a 0.1mm electrode to 46.5 [36-55]ms
- 1171 with a 0.5mm electrode in an area of fat, and from 32 [28-36]ms with a 0.1mm electrode to 35 [32-41]ms with a
- 1172 0.5mm electrode in a scar area. Although voltages and duration of bipolar EGMs also showed a similar tendency to
- 1173 increase as the mini-electrode size became larger, this was not significant in the scar tissue (voltage: P=0.51, duration:
- 1174 P=0.06). In other tissues, a particularly large difference was identified between the 0.2mm electrode and the 0.5mm
- electrode both in voltage and duration.
- Although N/F-ratio showed a tendency to decrease from 4.34 [2.52-6.82] with a 0.1mm-electrode to 3.79 [1.96-6.88]
- 1177 with a 0.5mm-electrode, the difference did not reach significance (P=0.68). G/S-ratio was largest in the 0.1mm-
- 1178 electrode (**Table 4-4-3**).
- 1179 Compared to these three catheters with different mini-electrodes, N/F ratio and G/S ratio was significantly larger in
- 1180 the mini-electrode with very micro-spacing catheter (0.2mm-electrode and 0.1mm spacing) (P<0.0001).
- 1181

| Unipolar EGM voltage (mV) | U1:0.1mm- electrode 3mm spacing | U2:0.2mm- electrode 3mm spacing | U3:0.5mm- electrode 3mm spacing | P values | B:0.2mm- electrode 0.1mm-spacing |
|------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------|--|
| All healthy (N=288) | 6.34 [4.06-8.90] | 7.38 [5.30-10.2] | 7.81 [5.63-10.5] | <0.0001 (#,\$) | 7.34 [5.47-10.0] |
| RA (N=72) | 4.89 [2.50-7.45] | 4.83 [2.83-7.32] | 5.20 [4.00-6.46] | | 4.69 [3.91-6.86] |
| LAA (N=72) | 8.08 [4.40-10.9] | 9.18 [7.42-11.2] | 10.03 [6.01-14.5] | | 8.67 [7.10-11.4] |
| LA (N=72) | 6.49 [4.29-9.85] | 9.02 [5.82-12.6] | 9.57 [7.85-14.0] | | 9.61 [7.05-11.4] |
| RV (N=72) | 6.59 [5.31-7.34] | 7.13 [6.19-8.38] | 7.15 [6.25-9.37] | | 6.88[5.77-8.98] |
| Fatty tissue (N=144) | 3.15 [1.77-4.88] | 3.657[2.34-4.86] | 4.92 [2.26-6.35] | <0.0001 (*,#,\$) | 3.60 [1.81-5.78] |
| RA (N=72) | 1.78 [1.10-3.36] | 2.59 [1.41-3.96] | 2.27 [1.53-5.26] | | 1.81 [1.52-2.54] |
| RV (N=72) | 4.88[2.78-5.55] | 4.68 [3.45-7.96] | 5.67 [4.92-6.77] | | 5.78 [5.17-6.53] |
| Scar tissue (N=72) | 2.5 [1.00-4.3] | 2.73 [1.91-3.36] | 3.59 [2.34-4.79] | 0.0005 (*,\$) | 3.13 [1.69-5.7] |
| LAA (N=36) | 0.78 [0.51-1.85] | 1.84 [1.17-2.07] | 2.1 [1.21-3.27] | | 1.54 [1.17-1.86] |
| RV (N=36) | 3.75 [2.49-4.42] | 3.17 [2.9-04.25] | 4.69 [3.68-5.51] | | 4.69 [3.19-6.59] |

Table 4-4-1. Unipolar EGM voltage

Significance difference (P<0.05) between U1 and U2 (*), U2 and U3 (#), and U1 and U3 (\$).

| Bipolar EGM Duration (ms) | U1:0.1mm- electrode 3mm spacing | U2:0.2mm- electrode 3mm spacing | U3:0.5mm- electrode 3mm spacing | P values | B:0.2mm- electrode 0.1mm-spacing |
|------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------|--|
| All healthy (N=288) | 34 [30-40] | 42 [37-48] | 49 [42-51] | <0.0001 (*,#,\$) | 43 [39-48] |
| RA (N=72) | 29 [24-34] | 39 [31-45] | 49 [39-50] | | 41 [34-44] |
| LAA (N=72) | 36 [31-41] | 47 [37-49] | 50 [40-52] | | 44 [38-47] |
| LA (N=72) | 33 [30-41] | 43 [39-49] | 48 [39-50] | | 46 [41-49] |
| RV (N=72) | 40 [36-49] | 41 [37-53] | 50 [45-60] | | 42 [40-54] |
| Fatty tissue (N=144) | 50 [41-53] | 50 [42-58] | 56 [51-63] | <0.0001 (*,#,\$) | 53 [45-58] |
| RA (N=72) | 46 [32-51] | 49 [42-56] | 53 [49-61] | | 49 [37-58] |
| RV (N=72) | 52 [44-56] | 54 [42-58] | 60 [54-64] | | 56 [49-60] |
| Scar tissue (N=72) | 43 [40-48] | 43 [38-50] | 51 [50-54] | <0.0001 (*,\$) | 43 [40-48] |
| LAA (N=36) | 40 [31-42] | 36 [32-45] | 50 [46-53] | | 40 [36-46] |
| RV (N=36) | 46 [44-52] | 45 [42-59] | 53 [50-56] | | 46 [42-58] |

Table 4-4-2. Unipolar EGM duration

1183

Significance difference (P<0.05) between U1 and U2 (*), U2 and U3 (#), and U1 and U3 (\$).

Table 4-4-3. Bipolar EGM voltage

| Bipolar EGM Voltage (mV) | U1:0.1mm- electrode 3mm spacing | U2:0.2mm- electrode 3mm spacing | U3:0.5mm- electrode 3mm spacing | P values | B:0.2mm- electrode 0.1mm-spacing |
|-----------------------------|---------------------------------------|---------------------------------------|---------------------------------------|------------------|--|
| All healthy (N=144) | 3.60 [2.37-4.74] | 3.84 [2.83-5.41] | 4.24 [3.42-5.78] | 0.0004 (#,\$) | 1.04 [0.74-1.44] |
| RA (N=36) | 3.54 [2.43-4.94] | 3.58 [2.36-5.27] | 3.36 [2.13-4.16] | | 1.09 [0.81-1.50] |
| LAA (N=36) | 4.21 [2.93-5.75] | 4.32 [3.47-5.07] | 4.53 [3.65-6.93] | | 0.93 [0.68-1.42] |
| LA (N=36) | 4.12 [3.39-5.45] | 4.91 [3.00-6.41] | 5.75 [4.16-7.25] | | 1.19 [0.73-1.47] |
| RV (N=36) | 2.41 [1.67-3.74] | 3.32 [2.15-5.07] | 4.16 [3.49-4.65] | | 0.98 [0.71-1.36] |
| Fatty tissue (N=72) | 0.87 [0.35-1.23] | 1.02 [0.47-1.70] | 1.05 [0.54-1.81] | 0.004 (#,\$) | 0.15 [0.10-0.25] |
| RA (N=36) | 0.88 [0.58-1.37] | 0.99 [0.42-1.43] | 0.94 [0.53-1.67] | | 0.12 [0.08-0.22] |
| RV (N=36) | 0.85 [0.33-1.17] | 1.04 [0.70-2.00] | 1.07 [0.55-2.13] | | 0.21 [0.13-0.43] |
| Scar tissue (N=36) | 0.54 [0.38-0.72] | 0.63 [0.38-0.82] | 0.63 [0.37-0.82] | 0.51 (-) | 0.09 [0.05-0.13] |
| LAA (N=18) | 0.63 [0.49-0.84] | 0.78 [0.66-1.01] | 0.80 [0.63-01.00] | | 0.09 [0.05-0.13] |
| RV (N=18) | 0.38 [0.31-0.81] | 0.42 [0.32-0.65] | 0.46 [0.23-0.64] | | 0.09 [0.05-0.13] |
| Non-fat/fat ratio | 4.34 [2.52-6.82] | 3.97 [2.30-6.17] | 3.79 [1.96-6.88] | 0.68 | 6.90 [4.20-15.8] |
| Gap/Scar ratio | 4.04 [2.02-6.03] | 2.81[1.81-4.28] | 3.10 [1.77-4.20] | 0.03 | 13.2 [5.93-20.9] |

1184

Significance difference (P<0.05) between U1 and U2 (*), U2 and U3 (#), and U1 and U3 (\$).

| Bipolar EGM Duration (ms) | U1:0.1mm- electrode 3mm spacing | U2:0.2mm- electrode 3mm spacing | U3:0.5mm- electrode 3mm spacing | P values | B:0.2mm- electrode 0.1mm-spacing |
|------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------|--|
| All healthy (N=144) | 26 [23-33] | 29 [26-33] | 31 [25-37] | 0.0004 (#,\$) | 23 [19-26] |
| RA (N=36) | 25 [19-28] 14-36 | 23 [20-28] | 31 [27-34] | | 20 [15-22] |
| LAA (N=36) | 30 [23-36] 15-45 | 32 [29-34] | 33 [25-40] | | 25 [20-28] |
| LA (N=36) | 27 [23-35] 14-42 | 32 [30-33] | 31 [24-39] | | 23 [20-30] |
| RV (N=36) | 29 [23-33] 19-54 | 29 [25-31] | 29 [25-31] | | 24 [19-28] |
| Fatty tissue (N=72) | 36 [29-44] 19-54 | 40 [36-55] | 47 [36-55] | <0.0001 (*,#,\$) | 32 [27-35] |
| RA (N=36) | 30 [26-36] 19-40 | 36 [32-39] | 36 [32-39] | | 27 [24-31] |
| RV (N=36) | 44 [34-49] 25-54 | 49 [44-53] | 55 [51-58] | | 35 [32-38] |
| Scar tissue (N=36) | 32 [28-36] 20-50 | 35 [30-37] | 35 [32-41] | 0.06 (-) | 29 [25-32] |
| LAA (N=18) | 29 [28-32] 23-40 | 31 [23-34] | 37 [31-40] | | 30 [26-31] |
| RV (N=18) | 32 [29-41] 20-50 | 36 [34-39] | 34 [32-43] | | 27 [24-33] |

Table 4-4-4. Bipolar EGM duration

1185 Significance difference (P<0.05) between U1 and U2 (*), U2 and U3 (#), and U1 and U3 (\$).

1186

1187 Summary and conclusion

1188 In the present study, we examine the impact of electrode size on EGMs, gap detection and far-field reduction and 1189 demonstrate that:

1190 1. Larger electrodes may increase the voltage and duration of unipolar EGMs.

1191 2. Larger electrodes may also increase the voltage and duration of bipolar EGMs.

1192 3. Although smaller electrode spacing may be better for gap detection and far-field reduction, smaller bipolar spacing

1193 may provide more impact.

1194

1195 We underscore the significance of electrode size on EGMs even with a mini-electrodes. Even with a same spacing,

center to center spacing may be different depending on the electrode size, which may affect the characterization ofEGMs. This concept should be considered in voltage mapping.

1198

1199 Manuscript is in submission

- 1200
- 1201

12025. Precise analysis of the circuit and mechanism of post-AF ATs mapped with1203novel high-resolution/high-density mapping system

- 1205 So far, the 'RhythmiaTM' mapping system with Orion basket catheter has provided a highest resolution/density map available in the market. Previously, the mechanism of post-AF AT analyzed without mapping system or with 1206 conventional low resolution/density mapping system was reported $^{27-29}$. Those reports demonstrate that in post-AF 1207 1208 ATs, MATs such as peritricuspid flutter (PTF), perimitral flutter (PMF), roof-dependent macroreentrant (RMAT) AT 1209 are commonest followed by microreentry and focal ATs. However, in these reports, the entire AT circuit is not always 1210 described in detail because of the low resolution of the mapping system or the absence of using 3D-EAM system. 1211 We hypothesized that analysis of post-AF ATs with higher resolution/density mapping system may demonstrate this circuit and clearly explain the mechanism of these ATs, leading to the identification of the critical and practical 1212 1213 isthmus to treat the AT. In this chapter, we analyzed a variety of post-AF ATs, using the 'RhythmiTM' mapping system, and demonstrate the 1214 1215 entire circuit and mechanism of ATs as well as showing the impact of using this system in terminating the AT.
 - 1216

1204

1217

RhythmiaTM mapping system

High resolution/high-density mapping system





- 1218
- 1219 Figure 5. RhythmiaTM high-reolution/high-density mapping system and Orion multipolar catheter 1220
- 1221

5-1. Re-visiting anatomical macroreentrant tachycardia after atrial fibrillation ablation using ultra-high-resolution mapping: implications for ablation.

1224

1225 Background and purpose of the study

1226 First, we focused the simplest type of post-AF AT, which is anatomical MAT (AMAT) including PTF, PMF and 1227 RMAT. We examined the complexity of the real AT circuits compared to those simply demonstrated in the past 1228 literature. Conventionally, when the diagnosis of AMATs was acquired, anatomical isthmuses were usually ablated 1229 (mitral isthmus (MI) at the lateral LA in PMF, LA roof in RMAT, and CTI in PTF). However, with the high 1230 resolution/high density mapping the practical isthmus may be different from those regions. We also compare the 1231 difference between the anatomical and practical isthmuses. The practical isthmus was anticipated to be the easiest 1232 and most appropriate site for ablation in the circuit, based on anatomical length, catheter stability, tissue thickness, 1233 nearby vulnerable structures, and preservation of atrial physiology, which was usually the narrowest bridge of 1234 conducting tissue between scars or anatomical obstacles. We hypothesized that the practical isthmus might be at a 1235 completely different location from the anatomical isthmus or a gap around the anatomical isthmus.



1236

1237 Figure 5-1. Practical isthmus and anatomical isthmus

(A) Type C perimitral flutter circuit detouring the lateral to anterior scars around the mitral annulus. Practical isthmus was not on the
anatomical isthmus (mitral isthmus), but the narrower isthmus between the previous ablation scars; (B) Type B roof-dependent
tachycardia circuit coexisted with localized reentrant circuit associated with the right PV. Practical isthmus was not on the anatomical
isthmus (roof), but the narrower isthmus between the previous ablation scar and septal mitral annulus.

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1243 Methods and Results

1244 In this study, we prospectively included 96 consecutive post-AF ablation AT patients undergoing ablation procedures 1245 guided by high-density mapping (RhythmiaTM) in our center between November 2014 and April 2016. Of these 1246 patients, 57 patients who had at least one anatomical MAT with a complete activation map during the procedure were

analyzed. In this cohort, we identified 75 anatomical MATs including 24 multiple-loop ATs which showed>2 active

1248 AT circuits. Totally, 88 anatomical MAT circuits including 16 peri-tricuspid circuits, 42 peri-mitral circuits, and 30

1249 roof-dependent circuits were analyzed.

- 1250 Although half of peri-tricuspid ATs had some parts of the circuit distant to the TA, the anatomical isthmus (CTI)
- 1251 corresponded to the practical isthmus. High-density mapping showed the gap in the low voltage area in the CTI as a
- 1252 practical is thmus which was significantly shorter than the anatomical CTI (14.6 ± 4.9 mm vs. 23.2 ± 5.0 mm, P=0.0001).
- 1253 AT was successfully terminated in all patients on the gap.
- 1254 Approximately 60% of peri-mitral ATs had a critical path of the circuit distant to the mitral annulus, and associated
- 1255 with low voltage areas around the annulus. Importantly, the practical isthmus was not in the anatomical isthmus
- (mitral isthmus on the lateral LA) in half of them. The practical isthmus was significantly shorter than the anatomical
 MI (16.1±8.1mm vs. 28.7±7.0mm, P<0.0001).
- 1258 Approximately 75% of roof-dependent ATs had circuits not rotating around both PV-pairs. Again, the practical
 - 1259 is thmus was not at the anatomical is thmus (LA roof) in 35% of them. The practical is thmus identified by high-density
 - 1260 mapping was significantly shorter than the anatomical isthmus (16.0±8.9mm vs 42.9±8.4mm, P<0.0001).

1261 Conclusions

- In conclusion, we found that the high-resolution/high density mapping successfully clarified the precise circuits of AMATs following AF ablation. Although the anatomical isthmus remained a suitable target in PTF, in the one-third of PMF and RMAT, shorter and more vulnerable isthmuses were identified and subjected to a tailored ablation and possibly easier ablation.
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Revisiting anatomic macroreentrant tachycardia after atrial fibrillation ablation using ultrahigh-resolution mapping: Implications for ablation ^(a)

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BACKGROUND Anatomic macroreentrant atrial tachycardias (MATs) are conventionally reported to depend on the cavotricuspid isthmus, the mitral isthmus, or the left atrial roof, and are commonly seen following catheter ablation for atrial fibrillation.

OBJECTIVES To define the precise circuits of anatomic MAT with ultrahigh-resolution mapping.

METHODS In 57 patients (mean age, 62 years; 10 female) who developed \geq 1 anatomic MAT, we analyzed 88 MAT circuits including 16 peritricuspid, 42 perimitral, and 30 roof-dependent circuits, using high-density mapping and entrainment.

RESULTS Of 16 peritricuspid atrial tachycardias (ATs), 8 (50.0%) showed a circuit not limited to the tricuspid annulus. However, cavotricuspid isthmus ablation terminated the tachycardia in all patients. Similarly, 26 of 42 perimitral ATs (61.9%) showed a circuit not limited to the mitral annulus, and a low-voltage zone <0.1 mV around the mitral annulus was associated with nontypical perimitral ATs (P < .0001). The practical isthmus was not in the mitral isthmus

Anatomic macroreentrant atrial tachycardias (MATs) are usually reported to be dependent on stereotyped isthmuses, at the cavotricuspid isthmus (CTI), mitral isthmus (MI), and left atrial roof. These arrhythmias are commonly seen following catheter ablation of atrial fibrillation (AF).^{1–4} Although the incidence of these anatomic MATs after AF ablation has been reported to be as high as 58%–100%,^{2,5–7}

in 13 of these 26 perimitral ATs (50%). Finally, 22 of 30 roof-dependent ATs (73.3%) had a circuit not rotating around both pairs of pulmonary veins. Brief assessment of the activation direction on the posterior wall in relation to that on the septal, anterior, and lateral wall helped deduce the circuit of roof-dependent AT in 27 of 30 (90.0%). Practical isthmus was not in the roof in 8 of 22 (36.4%). Practical isthmuses mapped with the system were significantly shorter than the usual anatomic isthmuses (16.1 \pm 8.2 mm vs 33.7 \pm 10.4 mm) (P <.0001).

CONCLUSIONS High-density mapping successfully identified the precise circuits and the practical isthmus of anatomic MATs in patients with prior atrial fibrillation ablation.

KEYWORDS Atrial fibrillation; Atrial flutter; Atrial tachycardia; Catheter ablation; Macroreentrant tachycardia

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the precise circuits of these MATs have not been described systematically. Entrainment and activation mapping are the fundamental techniques for identifying the critical path of the reentrant circuit.⁸ However, after multiple AF procedures, tachycardia circuit frequently follows a complicated course between prior ablation scars or fibrotic areas, and it is not easy to demonstrate the entire atrial tachycardia (AT) circuit

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Figure 1 A: Three types of peritricuspid atrial tachycardia (AT). A typical circuit proceeded around the tricuspid annulus (TA) and is defined as type A. A circuit of type B includes the entire TA and some additional track, and a type C circuit uses part of the TA but also depends on an extra path to return to the cavotricuspid isthmus (CTI). B: Three types of perimitral AT. Perimitral AT circuits are classified into 3 types in a similar manner to those of peritricuspid AT. C: Three types of roof-dependent AT. Typical roof-dependent macroreentrant atrial tachycardia (MAT), rotating around both pairs of pulmonary veins (PVs), is defined as type A, whereas type B rotates only around the right PVs and type C only around the left PVs. Black points indicate manual annotation of the lines of block; a line of block is defined as the lesion where the activation is completely stopped on the front, detouring around the lesion.

with only entrainment mapping. Furthermore, previously available mapping systems and catheters may not have had a sufficient resolution to demonstrate the complex activation sequence of all MATs. We hypothesized that a novel ultrahigh-density mapping system might provide a better description of the complicated circuits, which could lead to a more tailored ablation strategy by targeting shorter and more vulnerable isthmuses.

Methods Study population

In this study, we prospectively included 96 consecutive post-AF ablation AT patients undergoing ablation procedures guided by high-density mapping (Rhythmia, Boston Scientific, Natick, MA) in our center between November 2014 and April 2016. Results from 57 patients who had ≥ 1 anatomic MAT with a complete activation map during the procedure were analyzed. All patients gave written informed consent according to the institutional guidelines of the University of Bordeaux Health System, which granted ethical approval for the study.

Electrophysiological study and mapping with Rhythmia

Antiarrhythmic medications were discontinued >5 half-lives prior to ablation. All patients underwent anticoagulation treatment for ≥ 1 month prior to ablation. Transesophageal echocardiography or contrast computed tomography was performed prior to the procedure to exclude atrial thrombus. An activated clotting time of >300 seconds was maintained throughout the procedure. A steerable decapolar catheter was placed in the coronary sinus (CS). ATs were mapped with the Orion multipolar basket catheter (Boston Scientific) and

Rhythmia system with a steerable long sheath (Agilis, St Jude Medical, St Paul, MN, or Zurpaz, Boston Scientific), and an activation map was created with automatic standard beat-acceptance criteria based on: (i) cycle length (CL) variation, (ii) activation time difference variations between the CS electrograms, (iii) catheter motion, (iv) electrogram stability, (v) catheter tracking quality, and (vi) respiration gating. The confidence mask parameter was tuned for each map to be just above the noise level, to allow visualization of low-voltage signals. In addition to activation mapping, entrainment mapping was also performed. For the diagnosis of anatomic MAT, entrainment mapping was performed at \geq 2 widely spaced sites in the macroreentrant circuit. A site was considered part of the circuit if the postpacing interval measured from the stimulation artifact to the return atrial electrogram was within 20 ms of the total CL.

Definition of anatomic MAT

Each anatomic MAT was classified into 3 types, according to the circuit as shown in Figure 1.

Anatomic or practical isthmus ablation

We defined anatomic isthmus width as the length between anatomic obstacles or pulmonary vein (PV)–encircling lesions, between the inferior vena cava and tricuspid annulus (TA) in peritricuspid AT, between the anterior edge of the left PV-isolation lesion and mitral annulus (MA) in perimitral AT, and between the left superior PV and the right superior PV in roof-dependent AT. The practical isthmus was anticipated to be the easiest and most appropriate site for ablation in the circuit, based on anatomic length, catheter stability, tissue thickness, nearby vulnerable structures, and preservation of atrial physiology, which was usually the narrowest bridge



Figure 2 Anatomic isthmus and practical isthmus. A: Type C perimitral flutter circuit detouring the lateral to anterior scars around the mitral annulus. The practical isthmus was not on the anatomic isthmus (mitral isthmus) but on the narrower isthmus between the previous ablation scars. B: A type B roof-dependent tachycardia circuit coexisted with a localized reentrant circuit associated with the right PVs. The practical isthmus was not on the anatomic isthmus (roof) but on the narrower isthmus between the previous ablation scars in Figure 1.

of conducting tissue between scars or anatomic obstacles. The practical isthmus may be at a completely different location from the anatomic isthmus or a gap around the anatomic isthmus (Figure 2).

The end point for ablation, irrespective of the type of isthmus selected, was to achieve bidirectional conduction block.^{9–12} PVs were reisolated when required. Radiofrequency energy was delivered using an irrigated 3.5-mm-tip ablation catheter (ThermoCool SF catheter, Biosense Webster, Diamond Bar, CA), with a power of 30–35 W and a cutoff temperature of 45°C.

Statistical analysis

Data are expressed as mean [plus or minus standard deviation (SD)] for continuous variables and as numbers and percentages for categorical variables. χ^2 analysis or the Fisher exact test were used for categorical variables, and an analysis of variance or Kruskal–Wallis test was used for continuous variables. *P* values <.05 were considered statistically significant.

Results

Patient characteristics and the outcome

The baseline characteristics of the 57 patients with anatomic MATs are shown in Table 1. All patients had undergone ≥ 1 previous ablation procedure (median 3 procedures, range 1-6 procedures) including PV isolation, either as a stand-alone procedure or combined with mapping and ablation of an AT. Fifty-four (94.7%) had undergone substrate modification during the previous procedure. In this cohort, we identified 75 anatomic MATs, including 24 multiple-loop ATs that showed >2 active AT circuits (Table 2). In total, 88 anatomic MAT circuits-16 peritricuspid circuits, 42 perimitral circuits, and 30 roof-dependent circuits-were analyzed. Activation maps of mean 15,350 points (SD 7638 points) were acquired in a mean of 14.8 minutes (SD 8.5 minutes). Six patients with roof-dependent MAT required manual annotations of local activation time, with a mean of 4.6 manually annotated points (0.04%).

Peritricuspid AT circuits

We identified 16 peritricuspid ATs, which were classified into 3 types as shown in Figure 1A and Table 3. Mean mapping time was 9.5 minutes (SD 6.9 minutes) and the mean number of mapping points was 9898 (SD 7736 points). Eight ATs (50.0%) were type A, 5 (31.3%) type B, and 3 (18.7%) type C. A low-voltage zone (LVZ) <0.1 mV was frequently observed on the CTI (13 of 16 circuits, 81.3%) or right atria appendage (7 of 16 circuits, 37.5%), which were not isolated but coincident with previous ablation regions. In type B, although the entire TA was included in the circuit, the part of the circuit around the TA accounted for only a mean of 67.1% (SD 6.2%) of the CL. In type C, 80% of the TA was included in the circuit, but activation around the TA accounted for only a mean of 51.8% (SD 3.0%) of the CL. Two cases were biatrial macroreentrant AT, and both the right and left lateral walls were included in the circuit and

| Table 1 | Baseline | characteristics |
|---------|----------|-----------------|
| Tuble 1 | Duscunc | characteristics |

| | N = 57 |
|--|-----------------|
| Age, y, mean \pm SD | 61.9 ± 8.8 |
| Gender, female, n (%) | 10 (17.5) |
| Prior procedures, n, mean \pm SD | 3 ± 1.1 |
| SHD, n (%) | 13 (22.8) |
| CHF, n (%) | 5 (8.8) |
| HT, n (%) | 24 (42.1) |
| DM, n (%) | 2 (3.5) |
| Stroke, n (%) | 3 (5.3) |
| CHA_2DS_2 -VASc score, mean \pm SD | 1.4 ± 1.2 |
| LVEF, %, mean \pm SD | 54.3 ± 10.8 |
| Index procedure | |
| PV isolation only, n (%) | 7 (12.3) |
| Stepwise ablation, n (%) | 29 (50.9) |
| CardioInsight-based ablation, n (%)* | 21 (36.8) |
| Ablation regions through previous procedures | |
| PV, n (%) | 57 (100) |
| RA, n (%) | 45 (78.9) |
| CTI, n (%) | 44 (77.2) |
| SVC, n (%) | 14 (24.6) |
| RA-appendage, n (%) | 7 (12.3) |
| Other RA areas, n (%) | 5 (8.8) |
| LA, n (%) | 51 (89.5) |
| Roof, n (%) | 35 (61.4) |
| Inferior LA, n (%) | 36 (63.2) |
| Septal LA, n (%) | 31 (54.4) |
| Lateral LA (including MI), n (%) | 43 (75.4) |
| Coronary sinus, n (%) | 21 (36.8) |
| LA appendage, n (%) | 11 (19.3) |
| Other I A areas n (%) | 12 (21.1) |

CHF = congestive heart failure; CTI = cavotricuspid isthmus; DM = diabetes mellitus; HT = hypertension; LA = left atrium; LVEF = left ventricular ejection fraction; MI = mitral isthmus; PV = pulmonary vein; RA = right atrium; SD = standard deviation; SHD = structural heart disease; SVC = superior vena cava.

*CardioInsight is manufactured by Medtronic, Minneapolis, MN.

the septal wall was not, which was confirmed by entrainment mapping (Supplementary video). In both cases, extensive ablation had been previously performed on the septum.

High-density mapping showed the gap in the low-voltage area in the CTI as a practical isthmus that was significantly shorter than the anatomic CTI (mean 14.6 mm, SD 4.9 mm vs mean 23.2 mm, SD 5.0 mm, P = .0001). AT was successfully terminated in all patients on the gap. The mean radiofrequency (RF) time until AT termination was 5.1 minutes with an SD of 4.6 minutes.

Table 2 Number of atrial tachycardias and circuits

| | ATs, n (%) (N = 75) | Circuits, n (%) (N = 88) |
|--|------------------------|-----------------------------|
| Anatomic MATs | 51 (68.0) | 88 (100) |
| Peritricuspid ATs | 14 (18.8) | 16 (18.2) |
| Perimitral ATs | 24 (32.0) | 42 (47.7) |
| Roof-dependent ATs | 13 (17.3) | 30 (34.1) |
| Multiple loop (including \geq 1 MAT) | 24 (32.0) | . , |

ATs = atrial tachycardias; MATs = macroreentrant atrial tachycardias. Thirteen of multiple loop atrial tachycardia include two macroreentrant circuits. In total, 88 macroreentrant circuits were analyzed.

| | Total (N = 16) | Type A (typical) (N = 8, 50.0%) | Type B (N = 5, 31.3%) | Type C (N = 3, 18.7%) | P value |
|--|-----------------|------------------------------------|-----------------------|-----------------------|---------|
| CL, ms, mean \pm SD | 294 ± 78 | 255 ± 21 | 320 ± 107 | 357 ± 87 | .14 |
| % of TA in the entire circuit, mean \pm SD | 94.8 ± 8.3 | 100 ± 0 | 95 ± 5 | 80 ± 7.1 | .003 |
| % of TA in the entire CL, mean \pm SD | 80.7 ± 20.9 | 100 ± 0 | 67.1 ± 6.2 | 51.8 ± 3.0 | .0007 |
| Dual-loop with perimitral AT, n (%) | 2 (12.5) | 0 (0) | 0 (0) | 2 (66.7) | .007 |
| Practical isthmus on CTI, n (%) | 16 (100) | 8 (100) | 5 (100) | 3 (100) | - |
| Anatomic isthmus width, mm, mean \pm SD | 23.2 ± 5.0 | 22.1 ± 3.6 | 23.8 ± 3.0 | 25.1 ± 3.5 | .46 |
| Practical Isthmus width, mm, mean \pm SD | 14.6 ± 4.9 | 12.7 ± 4.7 | 14.3 ± 4.6 | 18.5 ± 3.8 | .25 |
| Signal voltage, mV, mean \pm SD | 0.59 ± 0.84 | 0.64 ± 1.15 | 0.33 ± 0.39 | 0.88 ± 0.17 | .68 |
| Signal duration, ms, mean \pm SD | 59 ± 14 | 60 ± 13 | 57 ± 20 | 60 ± 9 | .95 |
| %TCL, mean \pm SD | 0.21 ± 0.07 | 0.23 ± 0.05 | 0.20 ± 0.09 | 0.18 ± 0.04 | .41 |
| LVZs around the TA, n, mean \pm SD | 1.6 ± 0.8 | 1.3 ± 0.5 | 2.0 ± 1.2 | 1.7 ± 0.6 | .28 |
| LVZ in CTI, n (%) | 13 (81.3) | 8 (100) | 4 (80.0) | 1 (33.3) | .049 |
| LVZ in non-CTI, n (%) | 8 (50.0) | 3 (37.5) | 3 (60.0) | 2 (66.7) | .6 |
| No LVZ around the TA, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |

CL = cycle length; CTI = cavotricuspid isthmus; LV = low voltage; LVZ = low-voltage zone; TA = tricuspid annulus; TCL = total cycle length. Other abbreviations are as in Tables 1 and 2.

Perimitral AT circuits

We identified 42 perimitral ATs, which were classified into 3 types as shown in Figure 1B and Table 4. The mean mapping time was 15.3 minutes (SD 8.5 minutes) and the mean number of mapping points was 15,798 (SD 7400 points). Sixteen perimitral ATs (38.1%) were type A, 6 (14.3%) type B, and 20 (47.6%) type C. The CL was longer in non-type A perimitral AT [mean 291 ms (SD 70 ms) vs mean 234 ms (SD 35 ms), P = .002]. In type B, although the entire MA was included in the circuit, the part of the circuit around the MA accounted for a mean of 52.1% (SD 16.3%) of the CL. In the type C, a mean of 68.4% (SD 16.0%) of the MA was included in the circuit, but mitral annular activation accounted for a mean of 51.1% (SD 15.2%) of the CL. We divided the area around the MA into 4 segments (anterior, septal, inferior, and lateral wall) and examined the distribution of LVZs <0.1 mV. The number of LVZs was significantly different among the 3 types (P < .0001) (Table 4 and Supplementary Figure S1). Five patients without LVZ (11.9%) all demonstrated a type A circuit. The CS was involved in the circuit in 2 maps (4.8%) (Supplementary Figure S2), and the vein of Marshall appeared to be involved in the circuit in 1 map (2.4%), whereas the right atrium was involved in 3 maps. A perimitral circuit was deduced with manual activation mapping with ablation catheter in types A and B, as the activation was along the MA and in a single direction, although there was a jump with double potentials where the activation detoured in type B. However, manual activation mapping was not possible in type C.

In half of the circuits of atypical perimitral flutter, the practical isthmus was not on the MI. It was found on the septum in 3 of 6 circuits in type B (50.0%), whereas in type C, it was on the septum (2 circuits), anterior wall (2 circuits), posterior

 Table 4
 Perimitral atrial tachycardia circuits

| | Total (N = 42, 100%) | Type A (typical) (N = 16, 38.1%) | Type B (N = 6, 14.3%) | Type C (N = 20, 47.6%) | P value |
|--|-------------------------|-------------------------------------|--------------------------|---------------------------|---------|
| CL, ms, mean \pm SD | 269 ± 65 | 234 ± 35 | 295 ± 111 | 289 ± 56 | .007 |
| % of MA in the entire circuit, mean \pm SD | 84.2 ± 19.1 | 100 ± 0 | 94.5 ± 9.8 | 68.4 ± 16.0 | <.0001 |
| % of MA in the entire CL, mean \pm SD | 69.9 ± 26.7 | 100 ± 0 | 52.1 ± 16.3 | 51.1 ± 15.2 | <.0001 |
| Dual-loop with peritricuspid AT, n (%) | 2 (5.0) | 0 (0) | 0 (0) | 2 (10.0) | .32 |
| Dual-loop with roof-dependent AT, n (%) | 8 (20.0) | 5 (31.3) | 1 (16.7) | 2 (10.0) | .27 |
| Practical isthmus on MI, n (%) | 28 (66.7) | 15 (93.8) | 3 (50.0) | 10 (50.0) | .01 |
| Anatomic isthmus width, mm, mean \pm SD | 28.7 ± 7.0 | 28.5 ± 8.1 | 30.8 ± 5.5 | 28.2 ± 6.6 | .71 |
| Practical Isthmus width, mm, mean \pm SD | 16.1 ± 8.1 | 16.6 ± 8.4 | 21.6 ± 9.3 | 14.1 ± 7.1 | .17 |
| Signal voltage, mV, mean \pm SD | 0.59 ± 0.75 | 0.61 ± 0.73 | 0.89 ± 1.09 | 0.48 ± 0.67 | .74 |
| Signal duration, ms, mean \pm SD | 82 ± 44 | 71 ± 30 | 102 ± 71 | 85 ± 43 | .72 |
| %TCL, mean \pm SD | 0.30 ± 0.13 | 0.30 ± 0.11 | 0.33 ± 0.18 | 0.30 ± 0.14 | .91 |
| Number of LVZs around MA, mean \pm SD | 1.4 ± 0.9 | 0.7 ± 0.6 | 1.2 ± 0.4 | 2.1 ± 0.7 | <.0001 |
| LVZ in a lateral MA, n (%) | 22 (52.4) | 7 (43.8) | 1 (16.7) | 14 (70.0) | .049 |
| LVZ in a septal MA, n (%) | 20 (47.6) | 1 (6.3) | 5 (50.0) | 14 (70.0) | .0001 |
| No LVZ around the MA, n (%) | 5 (11.9) | 5 (31.3) | 0 (0) | 0 (0) | .01 |

MA = mitral annulus. Other abbreviations are as in Tables 1 and 3.

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Table 3 Peritricuspid atrial tachycardia circuits

wall (1 circuit), inside the CS (1 circuit), ridge between left appendage and left PV (2 circuits), or at the CTI (2 circuits). AT was successfully terminated in 31 of 42 cases (73.8%) and changed to another circuit in 5 of 42 cases (11.9%) in a mean of 9.0 minutes (14.6 minutes) of RF. The practical isthmus was at the MI in the remaining 6 circuits. The practical isthmus was significantly shorter than the anatomic MI [mean 16.1 mm (SD 8.1 mm) vs mean 28.7 mm (SD 7.0 mm), P < .0001]. We failed to achieve complete bidirectional block in 3 MI ablations (7.1%).

Roof-dependent AT circuits

We identified 30 roof-dependent ATs, which were classified into 3 types as shown in Figure 1C and Table 5. The mean mapping time was 16.3 minutes (SD 9.3 minutes) and mean number of mapping points 17,656 (SD 7335 points). Eight circuits (26.7%) were type A, 13 (43.3%) type B, and 9 (30.0%) type C. Eight circuits were dual loop with a perimitral second loop; most of these dual-loop circuits included the type C circuit, which turned around left PVs. We divided the left atrium into 5 segments (septal, anterior, lateral, posterior-inferior wall, and the roof) and examined the distribution of LVZs <0.1 mV. Although the number of LVZs was similar among the 3 types, type B more frequently showed an LVZ on the septum than the others did [11 of 13 cases (84.6%) vs 8 of 17 cases (47.1%), P = .05]. The activation direction during each roof-dependent AT is shown in Table 6 and Supplementary Figure S3. In type A, activation of both the anterior and septal walls was in the opposite direction to the posterior wall except for in 1 case. In type B, the activation of the posterior wall was mostly in the opposite direction to the septum, but not in the anterior or lateral walls. There were 3 circuits that demonstrated a figure-of-eight around the superior and inferior right PVs, using the PV carina as a common isthmus. Here the activation on the posterior and septal wall depended on the location of the PV gap.

Table 5 Roof-dependent atrial tachycardia circuits

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In type C, the activation of the posterior wall was mostly in the opposite direction to the lateral wall, but not in the anterior or septal walls.

The practical isthmus was on the roof for all type A circuits. However, this wasn't the case in 3 type B (23.1%) and 5 type C (55.6%) circuits. In type B, the PV carina was the practical isthmus. Type C frequently coexisted with perimitral AT (6 of 10 cases, 60.0%), and the MI was the common and practical isthmus. AT was successfully terminated in 19 of 30 cases (63.3%) and changed to another circuit in 9 of 30 cases (30.0%) using a mean of 8.7 minutes (SD 12.8 minutes) of RF. In the remaining 2 ATs, the MI was targeted as the common isthmus of dual-loop MATs.

The practical isthmus identified by high-density mapping was significantly shorter than the anatomic isthmus (16.0 \pm 8.9 mm vs 42.9 \pm 8.4 mm, *P* < .0001).

Ablation outcome

At the 6-month follow-up, 15 patients (26.3%) had AT recurrence; index ATs in these patients were peritricuspid AT in 3, roof-dependent AT in 5, perimitral AT in 4, and dual-loop AT with the combination of perimitral and roof-dependent circuits in 3 patients. In all patients with prior peritricuspid AT, the CTI had been ablated. Two of these patients had a repeat procedure, which demonstrated a different AT and bidirectional CTI block. Of 5 patients with prior roof-dependent AT, the LA roof had been ablated in the index procedure. Of these patients, 3 had undergone a repeat procedure, which demonstrated the reconnection across the roofline. Of 4 patients with prior perimitral AT, the MI had been ablated in the index procedure in 3 of them. One had undergone a repeat procedure identifying reconnection across the MI. Of 3 patients with prior dual-loop AT, the MI had been ablated in 2. One had undergone a repeat procedure with the reconnection across the MI.

| | Total (N = 30) | Type A (typical) (N = 8, 26.7%) | Type B (N = 13, 43.3%) | Type C (N = 9, 30.0%) | P value |
|--|-----------------|------------------------------------|---------------------------|--------------------------|---------|
| CL, mean \pm SD | 261 ± 57 | 263 ± 34 | 275 ± 65 | 241 ± 63 | .11 |
| Dual-loop with perimitral AT, n (%) | 8 (26.7) | 0 (0) | 2 (15.4) | 6 (66.7) | .004 |
| Practical isthmus on left atrial roof, n (%) | 22 (73.3) | 8 (100) | 10 (76.9) | 4 (44.4) | .032 |
| Anatomic isthmus width, mm, mean \pm SD | 42.9 ± 8.4 | 42.6 ± 6.1 | 43.3 ± 8.4 | 42.9 ± 10.8 | .98 |
| Practical Isthmus width, mm, mean \pm SD | 16.0 ± 8.9 | 17.6 ± 9.9 | 13.3 ± 6.4 | 18.5 ± 11.0 | .36 |
| Signal voltage, mV, mean \pm SD | 0.32 ± 0.48 | 0.15 ± 0.07 | 0.13 ± 0.09 | 0.73 ± 0.72 | .004 |
| Signal duration, ms, mean \pm SD | 89 ± 42 | 80 ± 29 | 107 ± 37 | 68 ± 46 | .06 |
| %TCL, mean \pm SD | 0.32 ± 0.11 | 0.30 ± 0.08 | 0.39 ± 0.08 | 0.25 ± 0.11 | .007 |
| Number of LVZs, mean \pm SD | 2.5 ± 1.1 | 2.4 ± 0.7 | 2.8 ± 0.9 | 2.1 ± 1.5 | .33 |
| LVZ in roof, n (%) | 25 (83.3) | 8 (100) | 11 (84.6) | 6 (66.7) | .18 |
| LVZ in septum, n (%) | 19 (63.3) | 2 (25.0) | 11 (84.6) | 6 (66.7) | .022 |
| LVZ in lateral wall, n (%) | 19 (63.3) | 4 (50.0) | 7 (53.9) | 8 (88.9) | .16 |
| LVZ in the other atrial walls (anterior or posterior), n (%) | 7 (23.3) | 3 (37.5) | 4 (30.8) | 0 (0) | .13 |
| No LVZ, n (%) | 1 (3.3) | 0 (0) | 0 (0) | 1 (11.1) | .30 |

Abbreviations are as in Tables 1 and 3.

| wall during root-depend | ient atrial tacr | iycardia | |
|--|--------------------------|---------------------------|--------------------------|
| | Type A, n (%) (N = 8) | Type B, n (%) (N = 13) | Type C, n (%) (N = 9) |
| Opposite activation direction in anterior wall | 7 (87.5) | 3 (23.1) | 5 (55.6) |
| Opposite activation direction in septal wall | 7 (87.5) | 12 (92.3) | 0 (0) |
| Opposite activation direction in lateral wall | 7 (87.5) | 0 (0) | 8 (88.9) |

| Table 6 | Activation direction in each wall compared with posterio |
|------------|--|
| wall durin | g roof-dependent atrial tachycardia |

Discussion

Major findings

We described the precise circuit and practical isthmus of post-AF ablation MATs. (i) Half of peritricuspid ATs had some parts of the circuit distant from the TA. However, AT was terminated on the CTI. (ii) Approximately 60% of perimitral ATs had a critical path of the circuit distant from the MA and associated with low-voltage areas around the annulus. Importantly, the practical isthmus was not in the MI in half of them. (iii) Approximately 75% of roofdependent ATs had circuits not rotating around both PV pairs. Again, the practical isthmus was not at the roof in 35% of them. The activation direction of the posterior and lateral or septal wall was helpful to conveniently deduce the circuit. (iv) Finally, high-density mapping allows us to identify an entire circuit and practical isthmus of these complex MATs.

The incidence of these anatomic MATs after AF ablation has been reported to be as high as 58%–100%.^{2.5–7} In these studies, activation and entrainment mapping, with or without 3-dimensional-mapping systems, were often performed to diagnose the tachycardia. Latcu et al¹³ described the mechanism of scar-related AT by using the Rhythmia system; they reported that a majority of MATs (71%) were perimitral flutter, roof-dependent, or double-loop reentry including a roof or a perimitral circuit. However, the precise circuit of these anatomic MATs has not been systemically described. In fact, post–AF ablation MATs are more complex, as demonstrated in the present study. Additionally, our study suggests that precise mapping allows for a tailored and easier ablation at the practical isthmus.

Precise circuits of peritricuspid AT

Peritricuspid AT after AF ablation is generally straightforward. Regardless of the distribution of the scar, the CTI was targeted with a linear lesion, because the CTI-line block is relatively easy to achieve. Interestingly, 2 cases of biatrial MATs were observed in our study. Mikhaylov et al¹⁴ reported 4 patients with biatrial ATs in whom biatrial-AT activation propagated in a clockwise direction around the MA across the lateral and inferior walls, entered the right atrium via the CS, traveled along the right septal wall, and returned to the left atrium over the upper anterior interatrial connection. In contrast, in our patients, the AT traveled around the tricuspid and MA as 1 large circuit. Because of extensive prior ablation on the septum, the activation map on both sides of the septum displayed either collision or block, and entrainment pacing also ruled out the septum as lying within the tachycardia circuit. The conduction between the left and right atrium is preserved through the Bachmann bundle and CS.¹⁵

Precise circuits of perimitral AT

Patel et al¹⁶ examined 17 AT patients after AF ablation using a multielectrode catheter and the EnSite-NavX system (St Jude Medical); in their report, they described 25 MATs, including 11 MATs that terminated on the MI, 9 on the roof, and 5 on the CTI, septum, lateral right atrium, or posterior left atrium. The mean number of acquired points was 365 (SD 108 points) despite the use of a multielectrode catheter; this was significantly fewer than the number of points in our study. Significantly higher point density in the present study may be an advantage to display precise AT circuits and practical isthmus. The number of LVZs around the MA may help to predict the type of perimitral AT. Although the conventional mapping approach may enable investigators to deduce the circuit of type A or B, this method is challenging in type C perimitral circuits, as part of the MA is activated in the opposite direction or the epicardial left atrium (the vein or ligament of Marshall and CS) or right atrium is involved.

Precise circuits of roof-dependent AT

For roof-dependent AT circuits, a simple 3-type classification is recommended. MAT turning around both ipsilateral PVs, right-ipsilateral PVs, or left-ipsilateral PVs. Conventionally, roof-dependent MAT is diagnosed by demonstrating the entire cycle within the LA around PVs and confirmed by entrainment mapping at 2 or more opposite sites.¹⁷ In addition, we previously reported the deductive mapping strategy to diagnose roof-dependent AT; in this strategy, the activation between the anterior and posterior walls is examined.³ In fact, opposite conduction directions in posterior and anterior walls may support the diagnosis of roof-dependent AT but only in type A cases. Among roof-dependent ATs, 75% turned around just 1 PV pair; then, the opposite conduction direction between the posterior and septal walls was seen in type B cases and the opposite conduction between the posterior and lateral walls was seen in type C cases. However, it should be underscored that some exceptions are seen because of the attenuation by the slow conduction or partial block due to previous ablation scars. For a convenient diagnosis, isolation of PVs including PV carina may prevent a misdiagnosis. As a consequence of prior ablation scars, the practical isthmus may be at the MI or at the PVs, even in roofdependent ATs rotating around 1 pair of ipsilateral PVs.

Clinical implications

This study with ultrahigh-density mapping demonstrates that anatomic MAT circuits after AF ablation are complex, especially when patients have complex prior ablation. The findings of the present study may be also useful for brief diagnosis with the conventional mapping catheter.

In anatomic MATs, it is mandatory not only to terminate the tachycardia but also to achieve complete block. High-resolution mapping may help tailor ablation to the most practical and vulnerable isthmus. However, further studies may be required to compare this tailored ablation with conventional anatomic ablation in these MATs. In addition, it would be of interest to assess the requirement for complete block in the anatomic isthmus after block is achieved in the practical isthmus, particularly when the anatomic isthmus showed low voltage.

Limitations

First, the findings in this study may not be generalized to ATnaive patients or post–AF ablation AT patients only with PV isolation, because atypical atrial flutter with different types of reentry circuits may be secondary to the extensive ablation with different strategies in the index or previous multiple ablation sessions, or even progressive remodeling. Second, in this study, we set the LVZ to <0.1 mV, following the previous study.¹⁸ However, regions of <0.1 mV may not always represent complete scar or block, because the scar threshold might be different due to smaller electrodes with smaller spacing in the Orion catheter. Finally, the difference in a mapping system and high-density mapping catheter may affect the result, which should be addressed in a future study.

Conclusion

High-resolution mapping successfully clarified the precise circuits of anatomic MATs following AF ablation. The anatomic isthmus remained a suitable target in peritricuspid AT. However, in the one-third of MI- and roof-dependent MAT, shorter and more vulnerable isthmuses were identified and subjected to a tailored ablation and possibly easier ablation.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2 017.10.029.

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5-2. A comprehensive multi-center study of the common isthmus in post AF ablation multipleloop atrial tachycardia

1290

1291 Background and purpose

- Dual-loop reentrant AT has been reported infrequently^{90,91}. Because of the lower resolution of the conventional mapping system, multiple-loop ATs may be underestimated. We hypothesized the prevalence would be much more higher in reality, and improvements in mapping systems and catheters allowed mapping with sufficient resolution to demonstrate the precise activation sequence of these complex ATs, which was not always possible with previously available mapping systems and catheters. In this chapter, we classify the type of multiple-loop ATs and compare the characteristics of common isthmus and ablation results.
- 1298 **Methods and results**
- 1299 In this study, we analyzed 193 consecutive patients with post-AF ablation in 4 centers between 2015 and 2016:
- 1300 Hôpital Cardiologique Haut Lévêque, Lyric institute, Université de Bordeaux; Hôpital Rangueil, Centre Hospitalier
- 1301 Universitaire de Toulouse; Jikei university school of medicine hospital, Tokyo, Japan; and Tsuchiura kyodo hospital,
- 1302 Ibaragi, Japan. Circuits and common isthmuses diagnosed by the high-resolution/high-density mapping system were
- 1303 analyzed in details as shown in the **Table 5-2-1**.

1304 **Definition**

- As previously reported, AMATs included PTF, PMF, and RMAT. Other reentrant ATs were all defined as non-AMAT
 in this study. Multiple-loop ATs were defined as those composed of more than 1 independent active circuits sharing
- 1307 one common isthmus including dual-loop ATs and triple-loop AT (Figure 5-2). In this study, dual-loop ATs were
- 1308 classified into 3 types: Type M, a combination of two AMAT; Type MN, a combination of one AMAT and one non-



AMAT; and Type N, a combination of two non-AMAT.

Figure 5-2. Classification of Multiple-loop AT Results and Summary

41 (21.2%) patients had 42 dual-loop ATs and 2 triple-loop ATs. Based on our classification of dual-loop ATs, shown in the Figure; 19 (43.2%) were Type M, 12 (27.9%) were Type MN and 11 (25.0%) were Type N. Two (4.5%) triple-loop AT demonstrated a combination of perimitral-AT, roof-dependent AT, and one non-anatomical AT. Thirty-three of 44 (75.0%) included at least one AMAT in the circuit, and 25/44 (56.8%) included at least one non-AMAT. Of the non-AMATs, 16/25 (64.0%) included at least one PV and 13/25 (52.0%) included a PV carina inside the circuit.

| Dual loop | |
|--|------------|
| AMAT-AMAT (type M) | 19 (43.2%) |
| Perimitral AT-roof-dependent AT | 19 (43.2%) |
| Non-AMAT-AMAT (type MN) | 12 (27.3%) |
| Non-AMAT-peritricuspid AT | 1 (2.3%) |
| Non-AMAT-perimitral AT | 7 (15.9%) |
| Non-AMAT-roof-dependent AT | 4 (9.1%) |
| Non-AMAT-non-AMAT (type N) | 11 (25.0%) |
| Triple loop | 2 (4.5%) |
| Perimitral AT-roof-dependent AT-non-AMAT | 2 (4.5%) |
| ATs including at least 1 AMAT | 33 (75.0%) |
| Perimitral AT | 26 (59.1%) |
| Roof-dependent AT | 23 (52.3%) |
| Peritricuspid AT | 1 (2.3%) |
| ATs including at least 1 non-AMAT | 25 (56.8%) |
| PV and PV-carina involved | 16 (36.4%) |
| PV-carina involved | 13 (29.5%) |
| PV noninvolved | 9 (20.5%) |
| | 1.1742 |

1326 Table 5-2-1. Characteristics of multiple-loop AT

The length of the common isthmus was 3.6+/-1.4 cm in Type M, 1.6+/-0.7cm in Type MN, and 1.1+/-0.7cm in Type N (P<0.0001). The area of the common isthmus was 12.92+/-7.68, 2.46+/-1.53, and 0.90+/-0.81cm2, in Type M, MN, and N (P<0.0001). The narrowest width of the common isthmus was 1.8+/-0.7cm, 1.1+/-0.3cm, and 0.7+/-0.3cm, in Type M, MN, and N (P<0.0001), respectively. The electrograms in the common isthmus showed longer duration and lower voltage in Type N, Type MN, and Type M (duration: 106+/-25ms, 87+/-27ms, and 69+/-27ms (P=0.006), and voltage: 0.06+/-0.02mV, 0.22 + -0.21 mVand 0.57+/-0.50mV (P<0.0001)) respectively. In total, the common isthmus was identified in approximately 90% of AT without any manual annotation, and this site was systematically targeted for the ablation site in Type N as shown in the

1343**Table 5-2-2.** On contrary, the common isthmus was not targeted for ablation in 30-40% Type M and Type MN1344(11/11(100%) in type N vs, 20/31(64.5%) in the other, P=0.03). The duration until the AT termination tended to be1345shorter in Type N compared to the others (median 1.3 min vs. 2,1 min, P=0.06).

| | Total | Type M (N=19) | Type MN (N=12) | Type N (N=11) | P Values | M vs MN; M vs N; MN vs N |
|--------------------------------|------------|---------------|----------------|---------------|----------|-----------------------------|
| Ablation on the common isthmus | 31 (73.8%) | 13 (68.4%) | 7 (58.3%) | 11 (100%) | 0.06 | 0.71; 0.06; 0.04 |
| Termination | 25 (80.6%) | 10 (76.9%) | 5 (71.4%) | 10 (90.9%) | | |
| Change | 4 (12.9%) | 1 (7.7%) | 2 (28.6%) | 1 (9.1%) | | |
| No effect | 2 (6.5%) | 2 (15.4%) | 0 (0%) | 0 (0%) | | |
| Ablation on the outer loop | 11 (26.2%) | 6 (31.6%) | 5 (41.7%) | 0 (0%) | 0.06 | 0.71; 0.06; 0.04 |
| Termination | 0 (0%) | 0 (0%) | 0 (0%) | | | |
| Change | 10 (90.9%) | 5 (83.3%) | 5 (100%) | | | |
| No effect | 1 (9.1%) | 1 (16.7%) | 0 (0%) | | | |
| AT recurrence at 1 y | 19 (45.2%) | 11 (57.9%) | 7 (58.3%) | 1 (9.1%) | 0.02 | 1.00; 0.02; 0.03 |

1347Table 5-2-2. Ablation details

Data are presented as n (%). AT indicates atrial tachycardia.

- 1348 Although ATs were not induced at the end of the procedure, 1 year follow-up demonstrated a relatively better outcome
- 1349 in Type N (P=0.02). In the re-do procedure, most cases showed mitral-isthmus related AT; out of 13 patients, mitral-
- 1350 isthmus was required to be ablated in 11 (84.6%) patients.
- 1351

1352 Summary and conclusion

1353 This multicenter study provides detailed and precise description of the entire circuit and the common isthmus of

1354 multiple-loop AT associated with post-AF ablation using the ultra-high density mapping system. We demonstrated 1355 that ;(1) Multiple-loop ATs were identified in approximately 20% in post-AF ablation AT. (2) One circuit of multiple-1356 loop reentrant atrial tachycardias was anatomical maroreentry in three-fourths of patients (using mitral isthmus and 1357 roof in more than half), while the remainder combined anatomical MAT and non-anatomical reentrant AT. (3) Half 1358 of multiple-loop ATs included non-anatomical reentrant circuit, 65% of them being associated with pulmonary veins 1359 (especially with the pulmonary vein carina). (4) The common isthmus was of smaller dimensions, with lower 1360 amplitude electrograms, when the arrhythmia combined two non-anatomical MATs. (5) Activation mapping with the 1361 Rhythmia system identified the correct circuit without manual annotation in approximately 90%. (6) The outcome 1362 was significantly better in Type N, and re-do procedures demonstrated that mitral isthmus was highly associated with 1363 recurrences.

1364

In conclusion, multiple-loop ATs are identified in 20% in post-AF ablation AT. These ATs frequently include anatomical MAT and PV (carina) -related AT as a circuit. Depending on the type of multiple-loop ATs, there is specific characteristics in the anatomical and electrophysiological common isthmuses. Although the ablation at the common isthmus was frequently successful, the long-term outcome was clearly worse when mitral isthmus was involved.

- 1370
- 1371

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1375

Comprehensive Multicenter Study of the Common Isthmus in Post-Atrial Fibrillation Ablation Multiple-Loop Atrial Tachycardia.

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Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Comprehensive Multicenter Study of the Common Isthmus in Post–Atrial Fibrillation Ablation Multiple-Loop Atrial Tachycardia

BACKGROUND: Characteristics of multiple-loop atrial tachycardia (AT) circuits have never precisely examined.

METHODS: In 193 consecutive post–atrial fibrillation ablation patients with AT, 44 multiple-loop ATs including 42 dual-loop AT and 2 triple-loop AT in 41 (21.2%) were diagnosed with the high-resolution mapping system and analyzed off-line.

RESULTS: In dual-loop ATs, 3 types were identified: type M, a combination of 2 anatomic macroreentrant ATs (AMATs) in 19 (43.2%); type MN, with 1 AMAT and 1 non-AMAT in 12 (27.3%); and type N with 2 non-AMATs in 11 (25.0%). The remaining 2 triple-loop ATs (4.5%) were a combination of perimitral-, roof-dependent-, and non-AMAT. At least 1 AMAT was included in 33 (75.0%), and 1 non-AMAT in 25 (56.8%). Of the ATs with at least 1 non-AMAT circuit, a pulmonary vein formed part of the circuit in 16/25 (64.0%). The length of the common isthmus was 3.6±1.4 cm in type M, 1.6±0.7 cm in type MN, and 1.1±0.7 cm in type N (P<0.0001). The area of the common isthmus was 12.92±7.68, 2.46±1.53, and 0.90±0.81 cm², in Type M, MN, and N (P<0.0001). The narrowest width of the common isthmus was 1.8±0.7 cm, 1.1±0.3 cm, and 0.7±0.3 cm in type M, MN, and N (P<0.0001), respectively. The electrograms in the common isthmus showed longer duration and lower voltage in type N, type MN, and type M (duration: 106±25 ms, 87±27 ms, and 69±27 ms; P=0.006; and voltage: 0.06±0.02 mV, 0.22±0.21 mV, and 0.57±0.50 mV; P<0.0001), respectively.

CONCLUSIONS: Multiple-loop ATs are complex, frequently including anatomic circuits. They have specific characteristics determined by the combination of AMAT and non-AMAT.

VISUAL OVERVIEW: An online visual overview is available for this article.

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The full author list is available on page 14.

Key Words: atrial fibrillation catheter ablation
conscious sedation
pulmonary veins tachycardia

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WHAT IS KNOWN?

• Dual-loop atrial tachycardias (ATs) in the left atrium after ablation for atrial fibrillation have been rarely reported, and the characteristics of these circuits have never examined in detail.

WHAT THE STUDY ADDS?

- Multiple-loop AT is not very a rare form of postatrial fibrillation ablation atrial tachycardia, and the entire circuit including common isthmus is successfully displayed by the high-resolution mapping system in most cases.
- Multiple-loop AT is simply classified to 3 categories: the combination of 2 anatomic macroreentrant ATs (43.2%), 1 anatomic macroreentrant AT and 1 nonanatomic reentrant AT (27.3%), and 2 nonanatomic reentrant ATs (25.0%). Anatomic obstacles (such as cavo-tricuspid isthmus, left atrium roof, and mitral isthmus) and pulmonary vein and pulmonary vein-carina are frequently included in the circuit.
- In dual-loop AT, the common isthmus was smaller, shorter, and narrower with electrograms of lower voltage, longer duration, and timed to the diastolic phase, when 1 of the 2 loops were nonanatomic.

ual-loop reentrant atrial tachycardia (AT) has

been reported infrequently.^{1,2} Most reports have focused on the postoperative patient,1 where dual-loop AT in right atrium seems to be common. More rarely, dual-loop ATs in the left atrium (LA) after ablation for atrial fibrillation (AF)³⁻⁶ have also been reported. Extensive fibrosis and ablation procedures in persistent AF may cause complex ATs. Improvements in mapping systems and catheters now allow mapping with sufficient resolution to demonstrate the precise activation sequence of these complex ATs, which was not always possible with previously available mapping systems and catheters. We used the Rhythmia mapping system with the 64-electrode Orion basket catheter (Boston Scientific, Marlborough, MA) to rapidly map complicated circuits with sufficient spatial resolution and electrogram quality to elucidate the entire circuit and particularly the critical isthmus in dual-loop ATs.

METHODS

To minimize the possibility of unintentionally sharing information that can be used to reidentify private information, the data, analytic methods, and study materials will not be made available to other researchers.

Study Population

The study population comprised consecutive patients with documented AT and prior AF ablation scheduled for treatment

guided by the Rhythmia high-resolution mapping system. Prior ablation was performed with a conventional 3-dimensional (3D) mapping system in all patients. Patients were identified in the following 4 participating centers between 2015 and 2016: Hôpital Cardiologique Haut Lévêque, Lyric Institute, Université de Bordeaux; Hôpital Rangueil, Centre Hospitalier Universitaire de Toulouse; Jikei University School of Medicine Hospital, Tokyo, Japan; and Tsuchiura Kyodo Hospital, Ibaraki, Japan. Patients with multiple-loop reentrant AT were included in the study. All data were prospectively collected during the procedure, and the anatomic and electrophysiological information of common isthmus was measured off-line in these specific ATs. All patients gave written informed consent according to the institutional quidelines, providing an ethical approval for the study.

Electrophysiological Study and Mapping With Rhythmia

Antiarrhythmic medications were discontinued >5 half-lives before ablation with the exception of amiodarone. All patients were anticoagulated for at least 1 month before ablation. Transesophageal echocardiography or contrast computed tomography was performed before the procedure to exclude atrial thrombus. Femoral venous access was performed under local anesthesia and conscious sedation. A steerable decapolar catheter was introduced within the coronary sinus. When patients were in sinus rhythm at the beginning of the procedure, AT was induced with burst pacing regardless of reconduction or block of previous pulmonary vein (PV) lesions or linear lesions. AT were mapped with the Orion multipolar basket catheter and Rhythmia system (Boston Scientific, Marlborough, MA) with a support of a steerable long sheath (Agilis-St. Jude Medical or Zurpaz-Boston Scientific), and activation map was created under the standard beat acceptance criteria (automatic) based on (1) cycle length (CL) variation, (2) activation time difference variations between the coronary sinus electrograms, (3) catheter motion, (4) electrogram stability, (5) catheter tracking quality, and (6) respiration gating. Before introducing the mapping catheter, heparin (100/IU per kg) was administered to achieve an activated clotting time of >300 s and maintained through the procedure. Although the dense scar threshold was nominally set at 0.03 mV as a confidence mask parameter, it was manually lowered to as close as possible to the noise threshold, to allow visualization of the entire circuit. We generally classified AT according to the activation pattern, namely focal AT, anatomic macroreentrant AT (AMAT), and non-AMAT.

Definition of Multiple-Loop AT

As previously reported,⁷ AMATs included peritricuspid AT dependent on the cavo-tricuspid isthmus, perimitral AT dependent on the mitral isthmus, and roof-dependent AT dependent on the left atrial roof. Other reentrant ATs were all defined as non-AMAT in this study. Multiple-loop ATs were defined as those composed of >1 independent active circuits sharing one common isthmus including dual-loop ATs (Figures 1 through 3) and triple-loop AT (Figure 4). Practically, the entire CL should be included in each of the multiple circuits. We performed entrainment pacing at both common isthmus and sites in the circuit apart from the common isthmus to confirm whether mapped locations lay within the

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Figure 1. Dual-loop reentry with the combination of 2 anatomic macroreentrant atrial tachycardias (AMATs; type M). A, Twelve-lead ECG showed a flutter wave without any isoelectric line. As shown in Movie I in the Data Supplement, the activation map demonstrated a figure of 8 circuit with the combination of perimitral circuit and a roof-dependent macroreentrant circuit (**B**–**D**). Dual circuits were shown in white and yellow arrows. The common isthmus (red arrow in **B**) was also visible with low voltage boundaries (0.06 mV) in the voltage map (**E**); the voltage and duration of the electrogram (EGMs) at the common isthmus (ablation site) were 0.21 mV and 69 ms, respectively (**F**). PPI indicates postpacing interval; and TCL, tachycardia cycle length.

activation circuit. When the local potentials were very small and the local tissue was difficult to capture, entrainment was performed not exactly on the common isthmus but at a site as close as possible to it. Postpacing interval (PPI)–tachycardia CL (TCL) ≤20 ms on the common isthmus and outer loop of each circuit was required for the diagnosis. In this study, dual-loop ATs were classified into 3 types: type M, a combination of 2 AMAT; type MN, a combination of 1 AMAT and 1 non-AMAT; and type N, a combination of 2 non-AMAT.

Measurement of the Circuit

The length of the entire circuit was measured on the geometry created by the Rhythmia system. The common isthmus was defined as the region where 2 wave fronts started to fuse up to the point where they split. The length, width, and area of each common isthmus were measured. In addition, common each isthmus was equally divided in 3 portions defined as entrance, mid, and exit. The electrogram voltage on the isthmus were measured. The electrogram voltage on the isthmus were measured. The edges of the common isthmus were defined as the boundaries bordering the activation front and calculated as the average values of the both edges.

Catheter Ablation Technique

In case of unstable AT or AF, resulting in difficulty in completing the activation map, PVs were reisolated and previous linear regions were completed if required. Otherwise, AT was mapped regardless of reconduction or block of previous PV lesions or linear lesions. Once the AT mechanism and circuit was diagnosed, the narrowest part of the common isthmus was targeted by creating a linear lesion between scars or anatomic obstacles. However, in some cases, the common isthmus was not targeted and each circuit was independently ablated because of the anatomic length, catheter stability, tissue thickness, and nearby vulnerable structures. When AT included AMATs, a linear lesion was completed at the relevant anatomic isthmus, even if the dualloop ATs were terminated with the specific common isthmus distant to the conventional anatomic isthmus. We confirmed complete lesion formation by demonstrating bidirectional conduction block using differential pacing.8 PVs were reisolated in case of reconnection. On completion of the procedure, we reconfirmed the end points of PV isolation and linear ablations, with an end-point of bidirectional conduction block. In addition, noninducibility of the tachycardia after ablation was confirmed. AT induction was performed by incremental burst pacing to a minimum pacing CL of 200 ms or the local effective refractory period of atrial tissue. We delivered radiofrequency energy using an irrigated 3.5-mm tip ablation catheter (ThermoCool SF, Biosense Webster, Diamond Bar, CA), with a power of 30 to 35 W and a cutoff temperature of 45°C.

Statistical Analysis

Data are expressed as mean (±SD) for continuous variables and percentages for frequencies. For comparisons between groups, χ^2 analysis or Fisher exact test was used for categorical

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Figure 2. Dual-loop reentry with the combination of 1 anatomic macroreentrant atrial tachycardia (AMAT) and 1 non-AMAT (type MN). A, Twelve-lead ECG showed a relatively longer P wave (194 ms) with a short isoelectric line (20 ms). As shown in Movie II in the Data Supplement, this dual-loop atrial tachycardia (AT) shows the combination of a roof-dependent macroreentrant circuit and relatively smaller circuit turning around a low-septal scar associated with the right inferior pulmonary vein (**B**, **C**). Dual circuits were shown in white and yellow arrows. The common isthmus (red arrow) was also displayed in the voltage map; the electrograms at the common isthmus (ablation site) are in the diastolic phase, and the voltage and duration are 0.06 mV and 122 ms, respectively (**D**). The border of the common isthmus is well demarcated (as white arrows in **B**) with a voltage of 0.05 mV. PPI indicates postpacing interval; and TCL, tachycardia cycle length.

variables. For continuous variables, the Kruskal–Wallis test was first performed and subsequently, the Dunnett T3 test was used for multiple comparisons. In view of the number of repeated tests, a *P* value <0.0125 was considered statistically significant. Triple-loop reentrant AT was not included in the analysis because of the small number of the cases (2 cases).

RESULTS

Patient Characteristics

Of 193 consecutive patients with post-AF ablation AT, 41 (21.2%) patients had 42 dual-loop ATs and 2 tripleloop ATs. The baseline characteristics of the 41 patients are shown in Table 1. The mean age of the cohort was 65.7±7.9 years. All patients had undergone at least 1 previous ablation procedure (mean, 2.7±1.4) including PV isolation, either as a stand-alone procedure or combined with mapping and ablation of an AT. Details of multiple-ATs are described in Tables 2 and 3. Based on our classification of dual-loop ATs, shown in Figures 1 through 3; 19 (43.2%) were type M, 12 (27.9%) were type MN, and 11 (25.0%) were type N. Two (4.5%) triple-loop AT demonstrated a combination of perimitral AT, roof-dependent AT, and 1 non-AMAT. Thirty-three of 44 (75.0%) included at least 1 AMAT in the circuit, and 25/44 (56.8%) included at least 1 non-AMAT. Of the non-AMATs, 16/25 (64.0%) included at least 1 PV and 13/25 (52.0%) included a PV carina inside the circuit. The activation maps performed with the Rhythmia system included 16270 \pm 7575 points mapped in 15.7 \pm 8.1 minutes. Manual reannotation was not required in 38/44 (86.4%) AT maps. Mean total ablation and procedure time was 35.5 \pm 15.0 minutes and 305.4 \pm 92.7 minutes.

Combination of 2 AMAT (Type M)

We identified 19/44 (43.2%) dual-loop ATs with a combination of 2 AMATs (perimitral flutter and roof-dependent AT in all cases). Mapping was performed in 14.3 \pm 8.5 minutes with 17237 \pm 8106 points, and the circuit including the common isthmus was identified without manual annotation in all cases. The mean circuit length was significantly different between the larger (17.7 \pm 2.3 cm) and smaller (16.1 \pm 2.1 cm) loop (*P*<0.0001). The perimitral circuit was generally longer than the roof-dependent circuit (17/19 [90.5%]). Perimitral flutter and roof-dependent AT shared the septal LA wall in 10 (52.6%) and the lateral LA wall in 9 (47.4%). Characteristics of the common isthmus were of area 12.92 \pm 7.68 cm², length 3.6 \pm 1.4 cm, and narrowest width 1.8 \pm 0.7 cm. The narrowest width in the common



A Twelve-lead ECG showed a relatively small P wave (128 ms) and long isoelectric line (192 ms). As shown in Movie III in the Data Supplement, the activation map demonstrated the dual-loop atrial tachycardia (AT) with a figure of 8 localized AT turning around a posterior scar (**B**, **C**). Dual circuits were shown in white and yellow arrows. Red arrow in **B** displays the common isthmus in the activation map; the electrograms at the common isthmus (ablation site) are in the diastolic phase, and the voltage and duration are 0.07 mV and 157 ms, respectively (**D**). In this case, the voltage on the circuit was generally low. The common isthmus was not clear in the voltage map, even when tuning the voltage range. PPI indicates postpacing interval; and TCL, tachycardia cycle length.

isthmus was at the exit in 12 (63.2%) patients. The mean duration was 69±27 ms and voltage 0.57±0.50 mV. The TCL-PPI was 6±7 ms on this site. The electrograms recorded in the common isthmus where timed to the diastolic phase in 8 (42.1%) ATs. The isthmus on the activation map could also be identified as a low voltage channel in all cases. The mean voltage of the barriers at the channel edge was 0.08±0.04 mV. The common isthmus was not targeted in 6/19 (31.6%). Instead, mitral isthmus and the roof was separately ablated, because the common isthmus on the septum was too long, or the roof/mitral isthmus gap was short enough with low voltage. When the common isthmus was targeted for ablation in 13/19 (68.4%), AT was terminated in 10/13 (76.9%) and changed to peritricuspid common flutter in 1/13 (7.7%) in mean 9.0±16.3 minutes (median, 2.7; 1.3–10.1 minutes). Common flutter was terminated by cavo-tricuspid isthmus linear ablation. In the remaining 2/13 (15.4%) ATs, the common isthmus on the septum was targeted without success, and the mitral isthmus and roof had to be ablated separately.

AT was not induced at the end of the procedure. However, during 1-year follow-up, 11 (57.9%) patients developed an AT recurrence; although 3 of them did not receive a redo procedure, 8 being reablated; 2 with PV carina-related AT, 3 with perimitral flutter including 1 with epicardial conduction on the ridge between left atrial appendage and left PVs, 2 with localized reentry around mitral isthmus, and 1 with localized reentry around the septum. A reconnected mitral isthmus was found in 6 patients and a reconnected roof in 1.

Combination of 1 AMAT and 1 Non-AMAT (Type MN)

We identified 12/44 (27.3%) dual-loop AT with the combination of 1 AMAT (perimitral flutter, peritricuspid flutter, or roof-dependent AT) and 1 non-AMAT. Mapping was completed in 18.2 ± 9.9 minutes with 19524 ± 7961 points. Two (16.7%) ATs required manual annotation in 22/17830 (0.12%) and 10/22013 (0.05%) to display the precise circuit and isthmus.

The PV was included in one of the circuits in 7/12 (58.3%). One of the dual-loop ATs involved a peritricuspid circuit, where the common isthmus laid between a septal right atrium scar and a tricuspid annulus. Seven ATs involved a perimitral AT circuit, where the common isthmus was on the mitral isthmus in 4, between anterior/septal scar and the mitral valve in 2, and the ridge between left atrial appendage scar and left superior pulmonary vein scar in 1. Four ATs involved a roof-dependent AT circuit, where the common isthmus was

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Figure 4. Triple-loop reentrant atrial tachycardia (AT).

As shown in Movie IV in the Data Supplement, this arrhythmia (12-lead ECG [A]) shows the combination of figure of 8 with a perimitral loop and a localized reentry around the previous ablation scar around the mitral isthmus. In addition, there is also a roof-dependent loop (**B**, **C**). Triple circuits were shown in white, yellow, and brown arrows. The common isthmus (red arrow) is also visible in the voltage map; the electrograms at the common isthmus (ablation site) are in the diastolic phase with the voltage and duration of 0.08 mV and 159 ms, respectively. Long fragmented signals are visible at the location where the localized reentry merges with the perimitral loop (**D**). The electrogram voltage at the edge of the channel is 0.07 m. PPI indicates postpacing interval; and TCL, tachycardia cycle length.

a gap in the previous right PV scars in 1, between posterior scars in 1, between septal scar and the mitral valve in 1 and the roof in 1. The AMAT circuit was long (17.2±3.4 cm) compared with non-AMAT circuit (10.7±3.4 cm; P<0.0001), and the anatomic circuit was larger in 11/12 (91.7%). The common isthmus metrics were area 2.46±1.53 cm², length 1.6±0.7 cm, and narrowest width 1.1±0.3 cm. The electrograms had a duration of 87±27 ms and a voltage of 0.22±0.21 mV. The TCL-PPI was 8±7 ms on this site. They were timed in the diastolic phase in 11 (91.7%). The isthmus on the activation map could be identified as a channel on the voltage map in all patients. The mean voltage of the barriers at the channel edge was 0.08±0.04 mV. The common isthmus was not always targeted, mostly based on operator's preference. The isthmus for 1 of the dual circuits was ablated in 5/12 (41.7%); for example, PVs, which were associated with one of the loops, were isolated first, changing the tachycardia. On the other hand, when the common isthmus was targeted for ablation in 7/12 (58.3%), in mean 5.0±5.3 minutes (median, 1.3; 1.2-8.3 minutes), AT was terminated in 5/7 (71.4%), and changed to AF in one, and peritricuspid common flutter in the other, which was terminated by cavo-tricuspid isthmus linear ablation.

AT was not induced at the end of the procedure. However, during the 1-year follow-up, 7(58.3%) patients developed an AT recurrence, and 5 patients received a redo procedure, all of them demonstrated mitral isthmus related AT and 2 included the same perimitral circuit as in the index procedure. Epicardial conduction around the mitral isthmus seemed to be associated with the recurrence in 2 of them.

Combination of 2 Non-AMATs (Type N)

We identified 11/44 (25%) dual-loop AT with a combination of 2 non-AMATs. Mean mapping time was 16.1 \pm 4.8 minutes with 11879 \pm 4344 points, and manual annotation was required around the isthmus region in 3 (27.3%) patients. The annotated points were 9/11880 (0.08%), 15/10769 (0.14%), and 9/8966 (0.10%). All but one circuit were a figure of 8. The isthmus area, length, and narrowest width were 0.90 \pm 0.81 cm², 1.1 \pm 0.7 cm, and 0.7 \pm 0.3 cm, respectively. The electrograms duration and voltage were 106 \pm 25 ms and 0.06 \pm 0.02 mV, respectively. The TCL-PPI was 3 \pm 5 ms. They occurred in the diastolic phase in all ATs. The common isthmus was in the PV or PV carina in 5, anteroseptal wall in 2, lateral wall (mitral

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| Table 1. Baseline Characteristics (M | (N=41) |
|--------------------------------------|--------|
|--------------------------------------|--------|

| Age, y | 65.7±7.9 |
|--|------------|
| Female | 12 (27.9%) |
| No. of prior procedure | 2.7±1.4 |
| SHD | 16 (36.4%) |
| Mitral valvular disease | 3 (7.3%) |
| Cardiovascular surgery | 0 (0%) |
| CHF | 11 (26.2%) |
| нт | 23 (52.3%) |
| DM | 3 (6.8%) |
| Stroke | 3 (6.8%) |
| CHA ₂ DS ₂ -VASc Score | 2.0±1.3 |
| LVEF, % | 52.6±11.0 |
| Previous AF type, persistent | 35 (85.4%) |
| Previous procedure for AF | 1.9±0.7 |
| PVI | 41 (100%) |
| Defragmentation in the LA | 28 (68.3%) |
| Roof line | 25 (61.0%) |
| Mitral isthmus line | 18 (43.9%) |
| CTI linear lesion | 22 (53.7%) |
| Maze procedure | 0 (0%) |

Data are presented as n (%) or mean (SD). AF indicates atrial fibrillation; CHF, congestive heart failure; CTI, cavo-tricuspid isthmus; DM, diabetes mellitus; HT, hypertension; LA, left atrium; LAV, left atrial volume; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; and SHD, structural heart disease.

isthmus region) 1, anterior portion of left appendage 1, ridge between left PV and left appendage 1, and posterior wall in 1. The isthmus could also be identified as a channel on voltage mapping in 5 (45.5%) ATs, and the mean voltage of the barriers at the channel edge was 0.05 ± 0.02 mV. Although a voltage channel was not clear on the voltage mapping in 6 (54.6%) patients, the isthmuses identified by the activation map were targeted for ablation, and AT terminated in 9 (81.8%), and changed in the remaining 2 cases in mean 1.5 ± 1.3 minutes (median, 1.3; 0.2-2.9 minutes).

No ATs were inducible at the end of the procedure. One (9.1%) patient developed an AT recurrence during 1-year follow-up but did not receive another procedure.

Comparison Between the 3 Types

In general, TCL tended to be longer (*P*=0.08) in type N, but the difference did not reach significance. In contrast, TCL variation was more frequently observed in type N compared with the other groups (*P*=0.009). P wave did not show specific characteristic between 3 groups. Isoelectric line tended to be longer in type N (113±69 ms in type M versus 130±105 ms in type MN versus 172±64 ms in type N), but the difference did not reach significance (*P*=0.06).

| Dual loop | |
|--|------------|
| AMAT-AMAT (type M) | 19 (43.2%) |
| Perimitral AT-roof-dependent AT | 19 (43.2%) |
| Non-AMAT-AMAT (type MN) | 12 (27.3%) |
| Non-AMAT-peritricuspid AT | 1 (2.3%) |
| Non-AMAT-perimitral AT | 7 (15.9%) |
| Non-AMAT-roof-dependent AT | 4 (9.1%) |
| Non-AMAT-non-AMAT (type N) | 11 (25.0%) |
| Triple loop | 2 (4.5%) |
| Perimitral AT-roof-dependent AT-non-AMAT | 2 (4.5%) |
| ATs including at least 1 AMAT | 33 (75.0%) |
| Perimitral AT | 26 (59.1%) |
| Roof-dependent AT | 23 (52.3%) |
| Peritricuspid AT | 1 (2.3%) |
| ATs including at least 1 non-AMAT | 25 (56.8%) |
| PV and PV-carina involved | 16 (36.4%) |
| PV-carina involved | 13 (29.5% |
| PV noninvolved | 9 (20.5%) |

Data are presented as n (%) or mean (SD). AMAT indicates anatomic macroreentrant atrial tachycardia; AT, atrial tachycardia; and PV, pulmonary vein.

About the common isthmus, anatomically, isthmus area, isthmus length, and narrowest width in the isthmus were significantly smaller in type N (P<0.0001), showing the tendency to increase in type MN and type M as shown in Table 4.

Electrophysiologically, electrogram duration became significantly longer (P=0.006) and voltage significantly lower (P<0.0001) from type M, to MN and N. Electrograms at the common isthmus laid in the diastolic phase in most of type N and type MN while it was in the systolic phase in 60% of type M (P=0.001). In general, mean TCL-PPI tended to be shorter on the common isthmus (6±6 ms) compared with on the outer loop (9±8 ms) although this did not reach statistical significance (P=0.07). Additionally, there was no significant difference between 3 groups in TCL-PPI on both the common isthmus (P=0.32) and the outer loop (P=0.15).

In total, the common isthmus was identified in \approx 90% of AT without any manual annotation, and this site was systematically targeted for the ablation site in type N as shown in Table 5. On the contrary, the common isthmus was not targeted for ablation in 30% to 40% type M and type MN (11/11 [100%] in type N versus 20/31 [64.5%] in the other, *P*=0.03). The duration until the AT termination tended to be shorter in type N compared with the others (median, 1.3 versus 2.1 minutes; *P*=0.06).

Although ATs were not induced at the end of the procedure, 1-year follow-up demonstrated a relatively better outcome in type N (P=0.02). In the redo pro-

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| | | | Circuit | 1 | Anatomic | Charact | eristics of CI | Electrophysiological Characteristics of Cl | | | | | |
|--------|----------|--------|---------------------------|-------------------|---------------|--------------|------------------------|--|------------------------|------------------|-----------------|--------|--|
| Group | ATCL, ms | Shape | Details of the Circuit | Common Isthmus | Length, cm | Area, cm² | Narrowest Width, cm | Narrowest Region | Edge Voltage, mV | Durations, mV | Voltages, mV | %TCL | |
| Type M | | | C1: perimitral | | | | | | | | | | |
| | 286 | of 8 | C2: roof- dependent | Septal LA | 4.99 | 13.60 | 1.10 | Exit | 0.09; 0.05 | 122 | 0.30 | 42.7 | |
| Type M | | Figure | C1: perimitral | | | | | | | | | | |
| | 210 | of 8 | C2: roof- dependent | Septal LA | 3.00 | 10.80 | 2.40 | Exit | 0.11; 0.11 | 47 | 1.10 | 22.4 | |
| Type M | | Figure | C1: perimitral | | | | | | | | | | |
| | 284 | of 8 | C2: roof- dependent | Septal LA | 3.15 | 4.97 | 1.60 | Exit | MV; 0.07 | 92 | 0.28 | 32.4 | |
| Type M | | Figuro | C1: perimitral | | | | | | | | | | |
| | 250 | of 8 | C2: roof- dependent | Septal LA | 3.43 | 11.00 | 1.75 | Exit | 0.09; 0.12 | 107 | 0.10 | 42.8 | |
| Type M | | Figure | C1: perimitral | Lateral I A | | | | | | | | | |
| | 220 | of 8 | C2: roof- dependent | (MI region) | 1.63 | 11.30 | 1.91 | Entrance | 0.09; 0.07 | 30 | 0.32 | 13.6 | |
| Type M | | Figure | C1: perimitral | Lateral I A | | | | | | | | | |
| | 190 | of 8 | C2: roof- dependent | (MI region) | 2.85 | 9.64 | 1.21 | Exit | MV; 0.13 | 28 | 2.00 | 14.7 | |
| Type M | Figure | Figure | C1: perimitral | Lateral I A | | | | | | | | | |
| | 203 | of 8 | C2: roof- dependent | (MI region) | 2.71 | 9.26 | 2.14 | Exit | MV; 0.06 | 69 | 0.21 | 34.0 | |
| Type M | NA. 4323 | Figure | C1: perimitral | Lateral I A | | | 010000000 | 00210- | | 0.02.020 | 201200 | 201000 | |
| | 210 | of 8 | C2: roof- dependent | (MI region) | 5.72 | 30.90 | 2.43 | Entrance | 0.08; 0.1 | 89 | 0.20 | 42.4 | |
| Type M | | Figure | C1: perimitral | Anterosental | | | | | | | | | |
| | 284 | of 8 | C2: roof- dependent | LA | 6.50 | 28.50 | 2.60 | Entrance | 0.04; 0.06 | 64 | 0.55 | 22.5 | |
| Type M | | Figure | C1: perimitral | Lateral LA | | 202203325 | | | | 1000 | 20.000 | | |
| | 231 | of 8 | C2: roof- dependent | (MI region) | 3.61 | 12.40 | 1.60 | Exit | MV; 0.1 | 48 | 0.26 | 20.8 | |
| Type M | | Figure | C1: perimitral | Lateral LA | | | | | | 0000 | - | | |
| | 333 | of 8 | C2: roof- dependent | (MI region) | 4.45 | 10.40 | 1.40 | Mid | 0.04; 0.04 | 84 | 0.12 | 25.2 | |
| Type M | | Figure | C1: perimitral | | | | | ~ | | | | | |
| | 310 | of 8 | C2: roof- dependent | Septal LA | 2.24 | 3.78 | 0.60 | Exit | 0.02; 0.03 | 86 | 0.11 | 27.7 | |
| Type M | | Figure | C1: perimitral | Lateral I A | | | | | | | | | |
| | 267 | of 8 | C2: roof- dependent | (MI region) | 3.88 | 8.84 | 2.20 | Exit | MV; 0.05 | 52 | 0.48 | 19.5 | |
| Type M | | Figure | C1: perimitral | Lateral I A | | | | | | | | | |
| | 240 | of 8 | C2: roof- dependent | (MI region) | 4.33 | 15.00 | 1.45 | Exit | 0.3; 0.08 | 74 | 0.92 | 30.8 | |
| Type M | | Figure | C1: perimitral | Lateral I A | | 20120200000 | | | | | | | |
| | 246 | of 8 | C2: roof- dependent | (MI region) | 5.93 | 20.00 | 2.67 | Entrance | 0.19; 0.1 | 45 | 0.96 | 18.3 | |
| Type M | | Figure | C1: perimitral | | | | | | | | | | |
| | 393 | of 8 | C2: roof- dependent | Septal LA | 2.39 | 6.08 | 1.00 | Entrance | 0.05; 0.03 | 88 | 0.08 | 22.4 | |

Table 2 Details of the Atrial Tachycardia (N-

(Continued)

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| | | | Circuit | 1 | Anatomic | Charact | eristics of CI | | Electroph | ysiological C | haracteristi | cs of Cl |
|---------|----------|------------------|---------------------------------------|---------------------------|---------------|--------------|------------------------|---------------------|------------------------|------------------|-----------------|----------|
| Group | ATCL, ms | Shape | Details of the Circuit | Common Isthmus | Length, cm | Area, cm² | Narrowest Width, cm | Narrowest Region | Edge Voltage, mV | Durations, mV | Voltages, mV | %TCL |
| Type M | | Finance | C1: perimitral | | | | | | | | | |
| | 218 | of 8 | C2: roof- dependent | Septal LA | 3.76 | 21.00 | 1.40 | Exit | 0.11; 0.08 | 41 | 0.88 | 18.8 |
| Type M | | Figure | C1: perimitral | | | | 3 | | | | | |
| | 336 | of 8 | C2: roof- dependent | Septal LA | 1.43 | 2.20 | 1.23 | Mid | 0.04; 0.04 | 97 | 0.95 | 28.9 |
| Type M | | Figure | C1: perimitral | | | | | | | | | |
| | 222 | of 8 | C2: roof- dependent | Septal LA | 3.04 | 15.80 | 3.40 | Exit | MV; 0.09 | 42 | 0.98 | 18.9 |
| Type MN | | Financia | C1: around RA septal scar | | | | | | | | | |
| | 290 | of 8 | C2: | Septal RA | 3.20 | 6.01 | 1.48 | Mid | 0.13; 0.13 | 54 | 0.81 | 18.6 |
| | | | peritricuspid | | | | | | | | | |
| Type MN | | Finite | C1: perimitral | Automotel | | | | | | | | |
| | 515 | of 8 | C2: around LA anteroseptal scar | LA | 0.71 | 2.09 | 0.74 | Entrance | 0.07; 0.07 | 117 | 0.05 | 22.7 |
| Type MN | | | C1: perimitral | | | | | | | | | |
| | 270 | Figure of 8 | C2: around LA posterior scar | Lateral LA (MI region) | 1.22 | 1.49 | 0.62 | Exit | 0.1; 0.15 | 86 | 0.10 | 31.9 |
| Type MN | | 2 | C1: perimitral | | | | | | | | | |
| | 200 | of 8 | C2: around LIPV | (MI region) | 1.65 | 1.25 | 0.82 | Exit | 0.09; 0.08 | 112 | 0.06 | 56.0 |
| Type MN | 0000000 | Figure | C1: perimitral | Lateral I A | 1000000 | where the | Starkings, | 1000 | 520 0 967 - 100 960 1 | 1000000 | 52.03.890 | |
| | 215 | of 8 | C2: around LIPV | (MI region) | 1.34 | 1.63 | 1.10 | Exit | 0.09; 0.05 | 56 | 0.25 | 26.0 |
| Type MN | 280 | Figure | C1: perimitral | Lateral LA | 1.22 | 2.04 | 1.20 | E.u. | 0.05.0.07 | 00 | 0.21 | 22.4 |
| | 280 | of 8 | C2: around LIPV | (MI region) | 1.33 | 2.04 | 1.20 | Exit | 0.05; 0.07 | 90 | 0.31 | 32.1 |
| Type MN | 205 | Figure | C1: perimitral | | 1.00 | 2.50 | 1.41 | Entrance | 0.00.0.05 | 70 | 0.14 | 20.5 |
| | 205 | of 8 | C2: around LA anterior scar | Anterior LA | 1.99 | 2.59 | 1.41 | Entrance | 0.08; 0.05 | /9 | 0.14 | 38.5 |
| Type MN | | - | C1: around | LA ridge | | | | | | | | |
| | 286 | Figure of 8 | C2: around | LAA and | 1.20 | 0.90 | 1.30 | Entrance | 0.17; 0.09 | 127 | 0.35 | 44.4 |
| | | | LPV | LPV | | | | | | | | |
| Type MN | | Daubla | C1: roof- dependent | | | | | | | | | |
| | 202 | circle | C2: around LA posterior scar | Posterior LA | 2.30 | 4.73 | 1.10 | Exit | 0.09; 0.15 | 56 | 0.24 | 27.7 |
| Type MN | | | C1: roof- dependent | | | | | | | | | |
| | 230 | Double circle | C2: around low-septal scar | Septal LA | 2.00 | 3.04 | 1.40 | Exit | 0.06; 0.04 | 75 | 0.17 | 32.6 |
| Type MN | 214 | Double | C1: roof- dependent | Sontal LA | 1 70 | 2.66 | 0.91 | Entroper | 0.07:0.05 | 100 | 0.05 | E7.0 |
| | 214 | circle | C2: around RIPV | Septal LA | 1.78 | 2.66 | 0.81 | Entrance | 0.07, 0.05 | 122 | 0.06 | 57.0 |

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| | | Circuit | | Anatomic Characteristics of CI | | | | | Electrophysiological Characteristics of Cl | | | |
|---------|----------|------------------|---|--------------------------------|---------------|--------------|------------------------|---------------------|--|------------------|-----------------|------|
| Group | ATCL, ms | Shape | Details of the Circuit | Common Isthmus | Length, cm | Area, cm² | Narrowest Width, cm | Narrowest Region | Edge Voltage, mV | Durations, mV | Voltages, mV | %TCL |
| Type MN | 234 | Double circle | C1: around RPV | 1.0 mm | 1.00 | 1.16 | 0.70 | Exit | 0.03; 0.03 | 71 | 0.06 | 30.3 |
| | | | C2: around RSPV | LA root | | | | | | | | |
| Type N | 369 | Figure of 8 | C1: around RSPV | 2014 | 2.56 | 2.99 | 1.08 | Mid | 0.03; 0.04 | 91 | 0.06 | 24.7 |
| | | | C2: around RIPV | KPV carina | | | | | | | | |
| Type N | 267 | Figure of 8 | C1, C2: around LA anteroseptal scar | Anteroseptal LA | 0.68 | 0.40 | 0.42 | Exit | 0.07; 0.06 | 110 | 0.09 | 41.2 |
| Type N | 302 | Figure of 8 | C1: around LIPV C2: around MI scar | Lateral LA (MI region) | 1.08 | 1.39 | 0.86 | Exit | U (<0.03) | 82 | 0.03 | 27.2 |
| Type N | 202 | Figure of 8 | C1: around RIPV | | 0.30 | 0.34 | 0.85 | Mid | 0.06; 0.07 | 102 | 0.09 | 50.5 |
| | | | C2: around RSPV | RPV carina | | | | | | | | |
| Туре N | 300 | Figure of 8 | C1: around LA anteroseptal scar C2: around LA anteroseptal scar | - Anteroseptal LA | 1.00 | 0.40 | 0.80 | Exit | U (<0.04) | 137 | 0.04 | 45.7 |
| Type N | 320 | Figure of 8 | C1: around LA posterior scar C2: around | Posterior LA | 0.70 | 0.40 | 0.43 | Exit | U (<0.07) | 157 | 0.07 | 49.1 |
| Type N | 242 | Figure of 8 | scar C1: around | e. | 1.30 | 0.90 | 1.10 | Mid | 0.05; 0.05 | 102 | 0.05 | 42.1 |
| 21 | | | RIPV scar C2: around RIPV scar | RIPV carina | | | | | | | | |
| Type N | 295 | Double circle | C1: around LAA circuit | | 0.50 | 0.48 | 0.90 | Exit | MV; 0.08 | 121 | 0.11 | 41.0 |
| | | | C2: around LAA ostial scar | Anterior LAA region | | | | | | | | |
| Туре N | 274 | Figure of 8 | C1: around LAA scar | | 2.30 | 0.38 | 0.30 | Mid | U (<0.05) | 89 | 0.05 | 32.5 |
| | | | C2: around LSPV | LA ridge | | | | | | | | |
| Type N | 320 | Figure of 8 | C1: around RSPV C2: around RIPV | RPV carina | 1.45 | 1.48 | 0.73 | Exit | U (<0.04) | 110 | 0.04 | 34.4 |
| Type N | 340 | Figure of 8 | C1: around RSPV C2: around RIPV scar | RPV anteroseptal region | 0.70 | 0.72 | 0.70 | Exit | U (<0.06) | 69 | 0.06 | 20.3 |

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| Group | ATCL, ms | Circuit | | Anatomic Characteristics of CI | | | | | Electrophysiological Characteristics of Cl | | | |
|----------------|----------|------------------------------------|---------------------------|--------------------------------|---------------|--------------|------------------------|---------------------|--|------------------|-----------------|------|
| | | Shape | Details of the Circuit | Common Isthmus | Length, cm | Area, cm² | Narrowest Width, cm | Narrowest Region | Edge Voltage, mV | Durations, mV | Voltages, mV | %TCL |
| Triple loop | | Figure of 8 Double circle | C1: perimitral | Lateral LA . (MI region) | 2.32 | 3.76 | 1.62 | Mid | 0.06; 0.07 | 159 | 0.08 | 45.7 |
| | 348 | | C2: roof- dependent | | | | | | | | | |
| | | | C3: around MI scar | | | | | | | | | |
| Triple loop | 225 | Figure of 8 Double circle | C1: perimitral | Septal LA | 1.61 | 2.22 | 0.90 | Exit | 0.06; 0.05 | 87 | 0.20 | 38.7 |
| | | | C2: roof- dependent | | | | | | | | | |
| | | | C3: around septal scar | | | | | | | | | |

ATCL indicates atrial tachycardia cycle length; C, circuit; CI, common isthmus; LA, left atrium; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LPV, left pulmonary veins; LSPV, left superior pulmonary vein; MI, mitral isthmus; MV, mitral valve; RA, right atrium; RIPV, right inferior pulmonary vein; RPV, right pulmonary veins; RSPV, right superior pulmonary vein; and U, unclear voltage channel.

cedure, most cases showed mitral isthmus related AT; out of 13 patients, mitral isthmus was required to be ablated in 11 (84.6%) patients.

Triple Loop

Two ATs demonstrated triple loop. In the first, the common isthmus was localized at the mitral isthmus region with 3 different circuits including a perimitral loop, a roof-dependent loop, and nonanatomic reentrant loop localized at the mitral isthmus scar. The isthmus area was 3.76 cm², length 2.3 cm, and the narrowest width 1.6 cm. The second triple loop had a common isthmus at the low-septal LA close to the mitral annulus with a perimitral loop, a roof-dependent loop, and a nonanatomic reentrant loop using a scar anterior to the right PVs. The isthmus area was 2.22 cm², length 1.6 cm, and narrowest width 0.9 cm. Electrophysiologically, electrograms in the common isthmus covered was 159 ms with a voltage of 0.06 mV in the first; and 87 ms and 0.20 mV in the second. Electrograms at the common isthmus were in the diastolic phase in both cases, and the AT terminated immediately during the ablation of the isthmus. At the end of the procedure, no AT was inducible, and none of them had AT recurrence during 1-year follow-up.

DISCUSSION Major Findings

This multicenter study provides a detailed and precise description of the entire circuit and the common isthmus of multiple-loop AT associated with post-AF ablation using the ultrahigh density mapping system. We demonstrated that (1) multiple-loop ATs were identified in $\approx 20\%$ in post-AF ablation AT. (2) One circuit of multiple-loop reentrant atrial tachycardias was ana-

tomic macroreentry in three-fourths of patients (using mitral isthmus and roof in more than half), whereas the remainder combined AMAT and non-AMAT. (3) Half of multiple-loop ATs included nonanatomic reentrant circuit, 65% of them being associated with PVs (especially with the PV carina). (4) The common isthmus was of smaller dimensions, with lower amplitude electrograms, when the arrhythmia combined 2 non-AMATs. (5) TCL variation was more remarkable in the combination of 2 non-AMATs. (6) The electrograms at the narrowest point of the common isthmus were in the diastolic phase when the circuit included a nonanatomic reentrant AT. (7) Activation mapping with the Rhythmia system identified the correct circuit without manual annotation in ≈90%. (8) Although a channel of preserved voltage between low voltage areas or anatomic obstacle was clearly visible in type M and MN, the channel may be unclear in type N. (9) The outcome was significantly better in type N, and redo procedures demonstrated that mitral isthmus was highly associated with recurrences.

Precise Circuit of Multiple-Loop ATs After AF Ablation

This study demonstrated that multiple-loop ATs were observed in $\approx 20\%$ of post-AF ablation AT and identified 3 categories. The combination of 2 AMATs (43.2%), 1 AMAT and 1 non-AMAT (27.3%), and 2 non-AMATs (25.0%). Additionally, 2 cases (4.5%) of triple-loop reentry were identified. The vast majority of multiple-loop (n=33, 75.0%) included 1 anatomic macroreentry and 25 (56.8%) included at least 1 nonanatomic reentrant AT. In the latter, PVs were included in the circuit in 16/25 (64.0%), and most of them also involved PV carina, which implied that not only PVs but also PV carina should have been isolated en block in the index procedure to

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| | Total | Type M (N=19) | Type MN (N=12) | Type N (N=11) | P Values | M vs MN; M vs N; MN vs N |
|---------------------------------------|------------|---------------|----------------|---------------|----------|-----------------------------|
| ATCL, ms | 269±64 | 260±54 | 262±87 | 294±46 | 0.08 | 1.0; 0.22; 0.61 |
| TCL variation >15 ms | 7 (16.7%) | 2 (10.5%) | 0 (0%) | 5 (45.5%) | 0.009 | 0.51; 0.07; 0.01 |
| Larger circuit length, cm | 15.0±5.3 | 17.7±2.3 | 17.2±3.4 | 8.0±4.4 | <0.0001 | 0.96; <0.0001; <0.0001 |
| Smaller circuit length, cm | 12.0±5.2 | 16.1±2.1 | 10.7±3.4 | 6.5±4.8 | <0.0001 | <0.0001; <0.0001; 0.08 |
| Shape of dual-loop | | | | | 0.02 | 0.02; 0.37; 0.32 |
| Figure of 8 | 37 (88.1%) | 19 (100%) | 8 (66.7%) | 10 (90.9%) | | |
| Double circle | 5 (11.9%) | 0 (0%) | 4 (33.3%) | 1 (9.1%) | | |
| Common isthmus (anatomic) | | | | | | |
| Area, cm ² | 6.78±7.67 | 12.92±7.68 | 2.46±1.53 | 0.90±0.81 | <0.0001 | <0.0001; <0.0001; 0.01 |
| Length, cm | 2.4±1.5 | 3.6±1.4 | 1.6±0.7 | 1.1±0.7 | <0.0001 | <0.0001; <0.0001; 0.27 |
| Width, cm | | | | | | |
| Entrance | 1.7±0.6 | 2.3±0.8 | 1.4±0.4 | 1.0±0.3 | <0.0001 | 0.001; <0.0001; 0.06 |
| Mid | 1.8±0.9 | 2.5±0.9 | 1.4±0.3 | 0.9±0.3 | <0.0001 | <0.0001; <0.0001; 0.008 |
| Exit | 1.5±0.8 | 2.0±0.8 | 1.2±0.4 | 0.9±0.6 | <0.0001 | 0.006; 0.001; 0.39 |
| Narrowest | 1.3±0.7 | 1.8±0.7 | 1.1±0.3 | 0.7±0.3 | <0.0001 | 0.001; <0.0001; 0.03 |
| Location of the narrowest isthmus | | | | | | |
| Narrowest=Entrance | 9 (21.4%) | 5 (26.3%) | 4 (33.3%) | 0 (0%) | | |
| Narrowest=Mid | 7 (16.7%) | 2 (10.5%) | 1 (8.3%) | 4 (36.4%) | | |
| Narrowest=Exit | 26 (61.9%) | 12 (63.2%) | 7 (58.3%) | 7 (63.6%) | | |
| Common isthmus (electrophysiological) | | | | | I | |
| Signal duration, ms | 84±30 | 69±27 | 87±27 | 106±25 | 0.006 | 0.21; 0.003; 0.24 |
| Signal voltage, mV | 0.34±0.41 | 0.57±0.50 | 0.22±0.21 | 0.06+/0.02 | <0.0001 | 0.03; 0.001; 0.08 |
| %TCL | 31.6±11.2 | 26.3±9.2 | 34.8±12.2 | 37.2±10.1 | 0.02 | 0.14; 0.02; 0.94 |
| Edge of the isthmus | | | | | | 1 |
| Unclear isthmus edge | 6 (14.3%) | 0 (0%) | 0 (0%) | 6 (54.6%) | <0.0001 | NA; 0.001; 0.005 |
| Edge including anatomic obstacle | 10 (23.8%) | 1 (9.1%) | 1 (8.3%) | 8 (42.1%) | 0.04 | 0.10; 0.10; 1.0 |
| Edge voltage, mV | 0.08±0.04 | 0.08±0.04 | 0.08±0.04 | 0.05±0.02 | 0.07 | 1.0; 0.03; 0.05 |
| TCL-PPI in the common isthmus, ms | 6±6 | 6±7 | 8±7 | 3±5 | 0.32 | 0.78; 0.68; 0.28 |
| Relation to the P wave | | 4 | 1 | | | 1 |
| Diastolic phase (outside P wave) | 30 (71.4%) | 8 (42.1%) | 11 (91.7%) | 11 (100%) | 0.001 | 0.008; 0.002; 1.0 |
| Early Diastolic | 3 (7.1%) | 0 (0%) | 2 (16.7%) | 2 (18.2%) | | |
| Mid diastolic | 20 (47.6%) | 6 (31.6%) | 8 (66.7%) | 6 (54.5%) | | |
| Late diastolic | 7 (16.7%) | 2 (10.5%) | 1 (8.3%) | 3 (27.3%) | | |
| Systolic phase (inside P wave) | 12 (28.6%) | 11 (57.9%) | 1 (8.3%) | 0 (0%) | | |
| Manual annotation for describing the | 5 (11.9%) | 0 (0%) | 2 (16.7%) | 3 (27.3%) | 0.07 | 0.14; 0.04; 0.64 |

Data are presented as n (%) or mean (SD). For the Dunnett T3 test, type MN is considered as a common control group. The comparison between M vs N is also kept to describe the detailed information. ATCL indicates atrial tachycardia cycle length; NA, not available; PPI, postpacing interval; and TCL, tachycardia cycle length.

prevent this type of ATs. Previously, one study³ described ATs in 78 patients after AF ablation using a conventional 3D mapping system. Seventeen patients (22%)

had dual-loop reentry: the combination of 2 AMATs in 4 (23.5%), the combination of AMAT and non-AMAT in 5 (29.4%), and the combination of 2 localized reentries in

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| | Total | Type M (N=19) | Type MN (N=12) | Type N (N=11) | P Values | M vs MN; M vs N; MN vs N |
|--------------------------------|------------|---------------|----------------|---------------|----------|-----------------------------|
| Ablation on the common isthmus | 31 (73.8%) | 13 (68.4%) | 7 (58.3%) | 11 (100%) | 0.06 | 0.71; 0.06; 0.04 |
| Termination | 25 (80.6%) | 10 (76.9%) | 5 (71.4%) | 10 (90.9%) | | |
| Change | 4 (12.9%) | 1 (7.7%) | 2 (28.6%) | 1 (9.1%) | | 9. |
| No effect | 2 (6.5%) | 2 (15.4%) | 0 (0%) | 0 (0%) | | |
| Ablation on the outer loop | 11 (26.2%) | 6 (31.6%) | 5 (41.7%) | 0 (0%) | 0.06 | 0.71; 0.06; 0.04 |
| Termination | 0 (0%) | 0 (0%) | 0 (0%) | | | |
| Change | 10 (90.9%) | 5 (83.3%) | 5 (100%) | 1918 | | |
| No effect | 1 (9.1%) | 1 (16.7%) | 0 (0%) | | | |
| AT recurrence at 1 y | 19 (45.2%) | 11 (57.9%) | 7 (58.3%) | 1 (9.1%) | 0.02 | 1.00; 0.02; 0.03 |

Data are presented as n (%). AT indicates atrial tachycardia.

1 (5.9%) patients. In this study, 2 (11.8%) patients with roof-dependent AT rotating around both PV were also included as a dual-loop AT, and the precise circuits were not described in the remaining 5 (29.4%) patients. The ultrahigh density mapping system allowed to delineate the precise incidence and mechanism of multiple-loop AT. In addition, we could simply classify these complex ATs and describe the anatomic and electrophysiological characteristics of the common isthmus in the present study.

Laţcu et al⁹ analyzed 33 AT with ultrahigh density mapping and reported 4 (12.1%) dual-loop ATs including 3 AT with the combination of roof-dependent and perimitral ATs and 1 AT combining a perimitral AT and an anterior localized reentry. The different prevalence may be attributed to the size of the study and different patient population. They included not only patients with post-AF ablation but also with previous surgical mitral valve repair. In addition, the present study included more persistent AF patients and substrate modification was more frequently performed. When dual-loop ATs included a nonanatomic reentrant circuit, the PVs were frequently involved. In addition, we would emphasize that even where both superior and inferior PVs were completely isolated, the PV-carina region between the PVs was frequently included in the circuit. From this point of view, circumferential PV isolation may be preferable than individual PV isolation.

There has been no study focusing specifically on dual-loop AT, possibly as a consequence of insufficient resolution from previous 3D mapping system generation. The ultrahigh density mapping system used here, with smaller and closely spaced electrodes may provide more precise information without the need for manual annotation in >90%.

Characteristics of the Common Isthmus and Ablation

The anatomic and electrophysiological characteristics of common isthmus were precisely investigated in

our study. The common isthmus was larger, longer, and wider in presence of 2 AMATs, as compared with when one or both loop was nonmacroreentrant. This isthmus was usually made of a channel of relatively preserved voltage (as for ventricular tachycardia channels^{10,11}), and voltage map were considered in addition to activation map to decide on the ablation strategy. Interestingly, the activation at the common isthmus was not always occurring during diastole. In general, mean TCL-PPI did not significantly differ between on the common isthmus and on the outer loop. In most cases, when the common isthmus of multiple-loop AT with AMAT circuits was located in the septum, the treating physician decided to ablate at the roof and mitral isthmus, because these regions had previously been ablated. In addition, catheter manipulation and therefore good contact can be difficult in the septal linear region, and ablation carries a risk of fast-pathway injury. In 2 cases, where the operator first targeted the common isthmus in the septum, ablation failed, and roof and mitral isthmus lines were separately completed. When 1 of the 2 loops were nonanatomic, the common isthmus was smaller, shorter, and narrower with electrograms of lower voltage, longer duration, and timed to the diastolic phase. When the 2 loops were nonanatomic reentrant ATs, the common isthmus was not always clearly visible as a voltage channel, even with high-resolution mapping. This is because manual reannotation around the critical isthmus was sometimes needed to better understand the map. However, ablation on the isthmus guided by the activation map was successful, even if the voltage channel was not clearly visible. We observed that special attention was to be used not to miss a nonanatomic loop when combined with a macroreentrant one, because the former was sometimes less obvious. This is important as it impacts the ablation strategy.

The most intuitive ablation strategy is to target the common isthmus. When the dual-loop ATs included a nonanatomic loop, the common isthmus was gen-

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erally short and the ablation was successful. When the arrhythmia combined 2 nonanatomic loops, a complete anatomic linear ablation was usually not needed, possibly accounting for the better outcome observed. On the contrary, when the dual-loop AT included 2 AMAT circuit, a complete anatomic isthmus block was required, but not always performed at the common isthmus, particularly when located in the septum.

Clinical Implications

We systematically describe the precise circuits and anatomic and electrophysiological characteristics of multiple-loop ATs after AF ablation. Most of these complex ATs involve at least 1 AMAT loop, but the PVs (especially the carina) are frequently involved. The identification of all the loops is critical to the ablation strategy which targets the common isthmus when at least 1 nonanatomic loops is involved. The common isthmus electrical activity occurs in diastole when such a nonanatomic loop is in the circuit but not systematically when the arrhythmia includes 2 anatomic loops. The ablation of the common isthmus directly terminates 80% of the ATs.

Limitations

First, because there were only 2 cases of triple-loop reentrant AT, they were not included in the statistics. Second, biatrial dual-loop ATs using the septum as a common isthmus may have been missed as once the entire CL was covered in the LA, the right atrium was not usually mapped. Third, whether the common isthmus was targeted or not might be an interesting topic in terms of the outcome of ablation. However, we could not mention this because the complete line of the anatomic isthmus was also achieved when low voltages because of the previous ablation was identified in those regions. Fourth, there is almost certainly an association between previous ablation regions and the subsequent AT circuit. However, this relationship is difficult to assess accurately in the present study because the details of previous ablations were taken from medical reports, and patient backgrounds were heterogeneous; the number of previous ablations differed and different 3D mapping systems and catheters were used. At a minimum, however, PV carina ablation was not part of the standard protocol in any of the institutions participating in this study. Fifth, the electrogram size and duration may be difficult to compare with previous mapping systems, because they are impacted by electrode size and spacing.¹¹ Finally, repeated statistical tests with a relatively small number of patients could have hidden the clinical impact in some clinical variables.

Conclusions

Multiple-loop ATs are identified in 20% in post-AF ablation AT. These ATs frequently include AMAT and PV (carina)-related AT as a circuit. Although the ablation at the common isthmus was frequently successful, the long-term outcome was clearly worse when mitral isthmus was involved.

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1396 5-3. Pulmonary vein-gap reentrant atrial tachycardia following atrial fibrillation ablation: an 1397 electrophysiological insight with high-resolution mapping

1398

1399 Background and purpose of the study

- PV-gap reentry is also sometimes seen after PV isolation, which is a type of reentrant AT involving the entrance and exit gaps on the previous PV isolation lines^{92,93}. Although previous reports demonstrated PV-gap reentrant AT (PVgap RAT) using a conventional 3D-EAM system, the mapping resolution and density were limited; thus, the detailed re-entrant circuit and electrophysiological characteristics of PV-gap RAT were not thoroughly investigated. In this study, we, therefore, assessed and clarified the detailed circuit and electrophysiological features of PV-gap RAT using
- 1405 the RhythmiaTM mapping system.

1406 Methods and Results

- 1407 In this study, we focused on PV-gap reentrant ATs and clarified the detailed circuit and electrophysiological features
- 1408 of them using the high resolution/density mapping system. This study was conducted as a multicenter study (6
- 1409 institutions). Among a total of 378 ATs in 281 patients, which were mapped using the RhythmiaTM system, 27 (7.1%)
- 1410 ATs in 26 (9.3%) patients that were diagnosed as PV-gap RATs. Pulmonary vein-gap RAT occurred during the first
- 1411 procedure in four patients, and after AF ablation in the remaining 22 patients. In 22 patients with prior ablation, PV
- 1412 isolation (segmental, n = 15; circumferential, n=7) had been successfully performed in all patients, and extended
- 1413 substrate ablations had been added in 15 patients [linear ablation, n=8; complex fractionated atrial electrogram
- 1414 (CFAE) ablation, n= 2, both linear and CFAE ablation, n=5].
- 1415 The circuit of PV-gap RAT was classified into three types as shown in the Figure 5-3: Type A, a small circuit around
- 1416 the unilateral PV (two gaps in one PV); Type B, a large circuit around the ipsilateral PV (two gaps in two PVs); and
- 1417 Type C, a huge circuit around the contralateral PV, which were based on the previous ablation lesions.



1418 Figure 5-3. A schematic diagram of a PV-gap RAT circuit

- 1419 Despite MATs, PV-gap RAT demonstrated a distinctive isoelectric interval in all leads, which is based on the fact that
- approximately 50% of the tachycardia cycle length time was spent within the PVs due to the presence of a double
- 1421 slow conduction zone (entrance and exit of the PV gaps). RhythmiaTM mapping demonstrated two distinctive entrance
- 1422 and exit gaps of 7.6 ± 2.5 and 7.9 ± 4.1 mm in width, respectively, the local signals of which showed slow conduction
- 1423 $(0.14 \pm 0.18 \text{ and } 0.11 \pm 0.10 \text{ m/s})$ with fragmentation (duration 86 ± 27 and 78 ± 23 ms) and low-voltage (0.17 ± 0.13
- and 0.17 ± 0.21 mV). Twenty-two ATs were terminated (mechanicalbump in one) and five were changed by the first
- radiofrequency (RF) application at the entrance or exit gap in 10 seconds ablating on the entrance or the exit of those
- 1426 gaps displayed by the RhythmiaTM. Compared to previous reports, the incidence of PV-related reentrant ATs in the
- present study is relatively higher. One main reason of this may be explained by a misdiagnosis between PV-RATsand PV focal ATs due to the low resolution/low density mapping used in the previous report.

1429 Summary and conclusion

- 1430 From the analysis from PV-gap RATs after AF ablation using a high-resolution mapping system, e have demonstrated
- that: (1) PV-gap RAT may be developed in approximately 10% of post-AF ablation ATs irrespective of a strategy of
 initial PV isolation (segmental or circumferential, or electrical or anatomical approaches) (2)The PV-gap RAT
- occurred through the two gaps on the previous PV isolation line in unilateral PVs as well as contralateral PVs. (3)
 Approximately 50% of the TCL time was spent inside the PVs with distinctive electrical features, including a critical
 isthmus showing slow conduction with fragmented and low-voltage signals. (4)High-resolution mapping guide
 ablation targeting the entrance or exit gap could effectively terminate AT.
- 1437 In conclusion, the novel ultra-high-resolution mapping system, 'RhythmiaTM', revealed the PV-gap RAT circuit in
- 1438 detail, and showed two gaps (entrance and exit) with distinctive electrophysiological features. The PV-gap RAT
- 1439 circuits were variable, and included macro- and localized re-entry that was associated with the previous ablation
- 1440 lesions. These could be simply and curatively treated with CA targeting the entrance or exit PV-gap with a guidance
- 1441 of this high-resolution mapping system
- 1442
- 1443
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- 1445

1446 **Pulmonary vein-gap re-entrant atrial tachycardia following atrial fibrillation ablation: an**

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- 1449 Yokoyama K, Tokuda M, Matsuo S, Naito S, Soejima K, Yoshimura M, Haïssaguerre M, Jaïs P, Yamane T.
- 1450

CLINICAL RESEARCH

European Society of Cardiology

Pulmonary vein-gap re-entrant atrial tachycardia following atrial fibrillation ablation: an electrophysiological insight with high-resolution mapping

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| Aims | The circuit of pulmonary vein-gap re-entrant atrial tachycardia (PV-gap RAT) after atrial fibrillation ablation is sometimes difficult to identify by conventional mapping. We analysed the detailed circuit and electrophysiological features of PV-gap RATs using a novel high-resolution mapping system. |
|------------------------|---|
| Methods and results | This multicentre study investigated 27 (7%) PV-gap RATs in 26 patients among 378 atrial tachycardias (ATs) mapped with Rhythmia TM system in 281 patients. The tachycardia cycle length (TCL) was 258 ± 52 ms with P-wave duration of 116 ± 28 ms. Three types of PV-gap RAT circuits were identified: (A) two gaps in one pulmonary vein (PV) (unilateral circuit) ($n = 17$); (B) two gaps in the ipsilateral superior and inferior PVs (unilateral circuit) ($n = 6$); and (C) two gaps in one PV with a large circuit around contralateral PVs (bilateral circuit) ($n = 4$). Rhythmia TM mapping demonstrated two distinctive entrance and exit gaps of 7.6 ± 2.5 and 7.9 ± 4.1 mm in width, respectively, the local signals of which showed slow conduction (0.14 ± 0.18 and 0.11 ± 0.10 m/s) with fragmentation (duration 86 ± 27 and 78 ± 23 ms) and low-voltage (0.17 ± 0.13 and 0.17 ± 0.21 mV). Twenty-two ATs were terminated (mechanical bump in one) and five were changed by the first radiofrequency application at the entrance or exit gap. Moreover, the conduction time inside the PVs (entrance-to-exit) was 138 ± 60 ms ($54 \pm 22\%$ of TCL); in all cases, this resulted in demonstrating P-wave with an isoelectric line in all leads. |
| Conclusion | This is the first report to demonstrate the detailed mechanisms of PV-gap re-entry that showed evident entrance and exit gaps using a high-resolution mapping system. The circuits were variable and Rhythmia TM -guided ablation targeting the PV-gap can be curative. |
| Keywords | Pulmonary vein-gap re-entry • Atrial tachycardia • Catheter ablation • High-resolution mapping • Atrial fibrillation • Rhythmia TM |

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What's new?

- The detailed circuit and electrophysiological features of pulmonary vein-gap re-entrant atrial tachycardia (PV-gap RAT) could be revealed by using the novel ultra-high-resolution mapping system (RhythmiaTM).
- The circuit of PV-gap RAT was classified into three types: a small circuit around the unilateral PV (two gaps in one PV), a large circuit around the ipsilateral PV (two gaps in two PVs), and a huge circuit around the contralateral PV, which were based on the previous ablation lesions.
- Despite macro-reentrant atrial tachycardia, PV-gap RAT demonstrated a distinctive isoelectric interval in all leads, which is based on the fact that approximately 50% of the tachycardia cycle length time was spent within the PVs due to the presence of a double slow conduction zone (entrance and exit PV gaps).
- RhythmiaTM-guided ablation targeting the PV gap can be curative for PV-gap RAT.

Introduction

Atrial tachycardias (ATs) often occur following catheter ablation of atrial fibrillation (AF),¹⁻³ the mechanism through which they occur is mainly scar-related re-entry due to the residual heterogeneous tissue from the prior ablation.¹ The circuits of scar-related AT after AF ablation are variable and are usually classified into macro- and localized re-entry according to the circuit size.¹ Pulmonary vein (PV)-gap reentry is also sometimes seen after PV isolation, which is a type of reentrant AT involving the entrance and exit gaps on the previous PV isolation lines.^{4,5} Although previous reports demonstrated PV-gap re-entrant AT (PV-gap RAT) using a conventional 3D-electroanatomical mapping (EAM) system,⁴ the mapping resolution and density were limited; thus, the detailed re-entrant circuit and electrophysiological characteristics of PV-gap RAT were not thoroughly investigated. We, therefore, assessed and clarified the detailed circuit and electrophysiological features of PV-gap RAT using a novel highresolution mapping system.

Methods

Study population

This was a multicentre study. A total of 378 ATs in 281 patients, which were mapped using a novel high-resolution mapping system (RhythmiaTM; Boston Scientific, Marlborough, MA, USA) in six high-volume centres in Japan and France were retrospectively enrolled. In the entire population, segmentally antral PV isolation and circumferential PV isolation were performed in 184 (65%) and 97 (35%) patients, respectively. Among the 378 ATs in 281 patients, 27 (7.1%) ATs in 26 (9.3%) patients that were diagnosed as PV-gap RATs were analysed in the present study.

Pulmonary vein-gap re-entrant atrial tachycardia occurred during or after ablation for AF in all cases. The present study was approved by the institutional review boards and ethics committees of each institution. All patients provided their written informed consent.

At mapping with RhythmiaTM and ablation procedures

All antiarrhythmic drugs were discontinued for at least five half-lives before the procedure with the exception of amiodarone. The ablation procedures were performed under conscious sedation or deep sedation, according to the centre. A multi-pole mapping catheter for the coronary sinus (CS) was positioned inside the CS via the right subclavian vein or right femoral vein and used as a reference for AT mapping. The left atrium (LA) was accessed via trans-septal puncture after a bolus administration of heparin. The target activated clotting time was set to 300-400 s during the procedure. During AT using a 64-pole mini-basket catheter ¹; Boston Scientific), activation mapping was performed using the (Orion^T RyhthmiaTM system. The beat acceptance criteria were regulated by the following six components, which are related to stability: cycle length (CL) (± 10 ms), propagation reference (± 5 ms), respiration ($\pm 10-15 \mu$ V), mapping catheter movement (±1 mm), electrogram stability (±25%), and tracking quality (±3 mm); mapping points were automatically acquired when all of these criteria were met. The projection distance and confidence mask were 2 mm and ${\sim}0.04\,\text{mV},$ respectively, and the confidence mask was manually lowered to as close as possible to the noise threshold to allow visualization of the entire circuit. The definitions of macro- and localized re-entry were the presence of a circuit of >3 cm and <3 cm in diameter, respectively,¹ in both, the local potentials along the circuit covered >90% of the tachycardia CL (TCL). In addition, when the postpacing interval (PPI) after entrainment pacing with a CL 10-20 ms shorter than the TCL was within 20 ms of the TCL, the pacing site was considered to be within the re-entry circuit.⁶ Pulmonary vein-gap re-entry was defined as re-entry showing a circuit through two gaps (entrance and exit gaps of PV) on the previous PV isolation lines. The entrance and exit gaps of the PV were recognized as isthmus channels showing slow conduction (conduction velocity <0.5 m/s). The entrance gap was defined as the site where the orthodromic wavefront enters the PV, while the exit gap was defined as the site where the orthodromic wavefront exits the PV. The types of PV-gap RAT circuit, the distribution of PV gaps (eight segments/ PV) and the electrophysiological features, including the width of the gap (isthmus), peak-to-peak bipolar electrogram amplitude, duration of the local signal, and conduction velocity on the entrance/exit gaps were analysed. The P-wave morphology was also assessed on 12-lead electrocardiography (ECG) during AT.

The ablation of PV-gap RATs was performed with the guidance of the activation map on the RyhthmiaTM system, that is, the entrance or exit site of the PV-gap was targeted during AT using a non-magnetic open-irrigated catheter (Celsius, ThermoCool, Biosense Webster, Inc., Diamond Bar, CA, USA) with a target temperature of 45°, a maximal power of 30–40 W, and an infusion rate of 17 mL/min. The termination of the PV-gap RAT was defined as the restoration of sinus rhythm (SR) or a change of the AT by radiofrequency (RF) ablation of the PV gap.

Follow-up

Patients were followed up with 12-lead ECG and 24-h Holter ECG in each outpatient clinic every 3–6 months. In addition, ambulatory ECG monitoring was performed when patients presented suspicious symptoms to detect recurrent arrhythmia. The primary endpoint was the recurrence of AT. Atrial tachycardia recurrence was defined as documented AT lasting >30 s after a blanking period of 3 months.

Statistical analyses

Quantitative data were expressed as the mean \pm standard deviation. For the comparison of continuous variables among three groups, a one-way ANOVA to compare parametric variables and the Kruskal–Wallis test was used to compare non-parametric variables. A regression analysis was performed to assess the correlation between two continuous variables. All tests were two-tailed, and P-values of <0.05 were considered to indicate statistical significance. All of the statistical analyses were performed using the MedCalc software package (version 11.2, MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics and previous ablation procedure

In this study population, the mean age was 63 ± 11 years, 8 (31%) of the patients were female, and CHADS₂ score was 0.7 ± 0.6 . All patients were initially diagnosed with AF (paroxysmal, n = 10; nonparoxysmal, n = 16) and referred for catheter ablation or surgical cryoablation. Echocardiogram showed $57 \pm 11\%$ of left ventricular ejection fraction and 42 ± 7.2 mm of left atrial diameter. Pulmonary vein-gap RAT occurred during the first procedure in four patients, and after AF ablation in the remaining 22 patients. In 22 patients with prior ablation, PV isolation (segmental, n = 15; circumferential, n = 7) had been successfully performed in all patients, and extended substrate ablations had been added in 15 patients [linear ablation, n = 8; complex fractionated atrial electrogram (CFAE) ablation, n = 2, both linear and CFAE ablation, n = 5].

At mapping

A total of 27 PV-gap RATs were identified in 26 patients, and the mean TCL was 258 ± 52 ms. All ATs were mapped with an OrionTM catheter based on the automated algorithm without manual annotation. The activation map was successfully obtained during AT without the interruption of sustained AT with a mean of 18596 ± 7434 mapping points with a mean mapping time of 19 ± 8 min. Entrainment mapping at >2 sites on the estimated circuit including inside PVs was performed in 17 (63%) ATs, which PPI was within 20 ms of the TCL in all cases. The visualized re-entrant circuit on the RhythmiaTM map could be successfully confirmed in all of these ATs and >90% of AT-CL were covered along the circuit in all ATs.

Electrophysiological characteristics of pulmonary vein-gap re-entrant atrial tachycardia circuits

Three types of PV-gap RAT circuit were identified (Figure 1) in the study population: Type A, two gaps in the same PV with a circuit around the unilateral PV (n = 17); Type B, two gaps in the ipsilateral superior and inferior PVs with a circuit around the ipsilateral PV (n=6); and Type C, two gaps in the same PV with a circuit around the contralateral PV (n = 4). The locations of the PV gaps were variable and are summarized in Table 1 and Figure 2. Type B PV-gap RATs always occurred during or after circumferential PV isolation, while all cases showing Type C had previously undergone ablation procedures with linear ablation in addition to PV isolation (Table 2). Localized reentry (<3 cm) was observed in 3 (11%) ATs. Representative cases of each type of PV-gap RAT are shown in Figure 3A-C and Supplementary material online, Movies. All cases of PV-gap RAT showed entrance and exit gaps on the PV antrum of 7.6 ± 2.5 and $7.9\pm4.1\,\text{mm}$ in width, respectively, which showed slow conduction with a conduction velocity of 0.14 ± 0.18 and $0.11\pm0.10\,m/s,$ continuous fragmented potential with a local signal duration of 86 ± 27 and 78 ± 24 ms and low-voltage with peak bipolar amplitude of 0.17 ± 0.13 and 0.17 ± 0.21 mV. In addition, the conduction time inside the PVs (entrance-to-exit) occupied $54 \pm 22\%$ (138 ± 60 ms) of the whole TCL (258 ± 52 ms). These electrophysiological features did not differ to a statistically significant extent among the three types of circuits (*Table 2*), and there were no differences between the entrance and exit gaps.

P-wave morphology during pulmonary vein-gap re-entrant atrial tachycardia

The maximum P-wave duration on 12-lead ECG was 116±28 ms, which covered 46±10% of the TCL, in addition all cases had an isoelectric line in all leads during AT. The P-wave polarity in lead V1 was positive in 16 (62%) ATs and biphasic (RS pattern) in the remaining 11 (38%); the inferior leads were variable (positive, n = 19; negative, n = 5; biphasic, n = 3). Interestingly, the maximum P-wave duration on the 12-lead ECG was moderately correlated with the activation time of the LA ($R^2 = 0.25$, P = 0.003) and isoelectric duration was also moderately correlated with the conduction time inside the PVs (entrance-to-exit) ($R^2 = 0.26$, P = 0.005) (*Figure 4*). In addition 76±24% of isoelectric line were correspond to conduction inside the PVs. On the other hand, there was no correlation between the anatomical direct distance from the entrance to exit site (39±21 mm) and the conduction time within the PV ($R^2 = 0.01$, P = 0.64).

Results of pulmonary vein-gap re-entrant atrial tachycardia ablation

Among 27 ATs, the exit gap was targeted in 13 (48%) ATs, while the entrance gap was targeted in the remaining 14 (52%) ATs with the guidance of a RhythmiaTM map. In total, 26 (96%) ATs were terminated by RF ablation targeting the gaps (SR restoration, n = 20; AT change, n = 5) in 10 ± 10 s; the remaining one AT was terminated by mechanical bump with an ablation catheter on the exit gap and was non-inducible thereafter. Four out of five ATs were converted to another ATs of different PV-gap re-entrant form in one, roof dependent form in two, mitral isthmus dependent form in one, and the remaining one was converted to unmappable AT but finally terminated into SR spontaneously. These four re-entrant ATs could be terminated by RF for PV gap or linear ablation. After the termination of ATs, re-PV isolation was successfully accomplished in all cases with the additional RF applications for the remaining gap during SR and bidirectional electrical conduction block between all PVs and the LA was confirmed using a circular mapping catheter. In total, the number of RF applications and RF time for the entrance and exit gaps including bonus RF applications were 2.4 ± 1.5 times and 117 ± 51 s at the first attempt gap (AT termination site), and 3.1 ± 4.8 times and 109 ± 118 s at the remaining gap, respectively. In all cases, at the end of the procedure, AT could not be induced from the CS by any programmed stimulation under the administration of isoproterenol. After 12 ± 7 months of follow-up, four patients had recurrent AT other than PV-gap RAT. Atrial fibrillation recurred in two patients and one patient had cerebral haemorrhage because of poor blood pressure control, unrelated to the ablation procedure.



Figure 1 A schematic diagram of a PV-gap RAT circuit. (A) Entrance and exit gaps are observed in the same PV. The re-entry circuit consists of a circuit around the ipsilateral PV (small unilateral circuit). (B) Entrance and exit gaps are observed in a different PV (the ipsilateral PV; e.g. entrance gap in the RIPV and exit gap in the RSPV), the macro-reentry circuit of which consists of a circuit around the ipsilateral PV (moderate large unilateral circuit). (C) Entrance and exit gaps are observed in the same PV, the macro-reentry circuits of which consists of a circuit around the ipsilateral PV (moderate large unilateral circuit). (C) Entrance and exit gaps are observed in the same PV, the macro-reentry circuits of which consist of a circuit around the contralateral PVs (large bilateral circuit). IPV, inferior pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, gap RAT, PV-gap re-entrant atrial tachycardia; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SPV, superior pulmonary vein; vein.





Discussion

Major findings

This is the first report to describe the detailed circuit of PV-gap RATs after AF ablation using a high-resolution mapping system. This multicentre study showed several important clinical implications: (i) PV-gap RAT could occur during or after PV isolation in significant cases, even when different methods of PV isolation were used (segmental or circumferential, or electrical or anatomical approaches); (ii) The PV-gap RAT circuits were variable, and were located around not only unilateral PVs but also contralateral PVs; (iii) PV-gap RAT occurred through the two gaps on the previous PV isolation line; these gaps had distinctive electrical features, including a critical isthmus showing slow conduction with fragmented and low-voltage signals; (iv) approximately 50% of the TCL time was spent inside the PVs, which resulted in a P-wave morphology with isoelectric line that could be distinguished in all leads; and (v) high-resolution mapping guide ablation targeting the entrance or exit gap could effectively terminate AT.



Figure 3 Typical examples of PV-gap RAT. (A) The entrance and exit gaps were identified on the top-posterior and bottom-posterior of the RSPV with a small circuit (<3 cm) rotating around the previous ablation lesion along the posterior aspect of the RSPV (Type A in *Figure 1*). (B) The entrance and exit gaps were identified on top of the LSPV and on the bottom of the LIPV with a moderate large circuit (<3 cm) rotating around the posterior wall of the LIPV (Type B in *Figure 1*). (C) The entrance and exit gaps were identified on the anterior and posterior of LSPV with a large circuit (>3 cm) rotating around the contralateral septal side (Type C in *Figure 1*). Of note, the roof and mitral isthmus lines were blocked by the previous ablation. LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV-gap RAT, pulmonary vein-gap re-entrant atrial tachycardia; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

5

| Patient number | Atrial tachycardia number | AT-CL (ms) | Entrance gap | Exit gap | Prior ablation | Circuit type |
|-------------------|------------------------------|------------|--------------|-------------|----------------------------|--------------|
| 1 | 1 | 278 | LS ant | LS post | sPVI + Roof/MI line | С |
| 2 | 2 | 202 | RS top | RS post | sPVI + Roof/MI line | A |
| | 3 | 226 | LI ant | LI post | sPVI + Roof/MI line | A |
| 3 | 4 | 225 | LI ant | LI top-post | sPVI + Roof/MI line + CFAE | С |
| 4 | 5 | 242 | LS bot | LS bot-post | sPVI + Roof/MI line | А |
| 5 | 6 | 240 | LS top | LS post | sPVI + Roof/MI line | С |
| 6 | 7 | 241 | RS top-ant | RS bot-ant | sPVI + Roof/MI line | A |
| 7 | 8 | 210 | RS bot | RS post | sPVI | A |
| В | 9 | 297 | RS post | RS ant | cPVI | А |
| 9 | 10 | 240 | RS top | RI bot | cPVI | В |
| 10 | 11 | 248 | LS top-pos | LS bot-pos | cPVI + Roof line | В |
| 11 | 12 | 252 | LS top | LI bot | cPVI | В |
| 12 | 13 | 299 | RI post | RI ant | PVI with surgical cryo | A |
| 13 | 14 | 243 | RI bot | RS top | cPVI | В |
| 14 | 15 | 219 | RS top | RS ant | cPVI | A |
| 15 | 16 | 369 | RS top | RS ant | sPVI + Roof line + CFAE | А |
| 16 | 17 | 278 | RS bot-post | RS bot-ant | sPVI + Roof/MI line + CFAE | А |
| 17 | 18 | 268 | LI post | LI ant | sPVI + CFAE | A |
| 18 | 19 | 344 | RS bot-post | RS ant | sPVI | A |
| 19 | 20 | 240 | LS bot-post | LI ant | cPVI | В |
| 20 | 21 | 232 | LC top | LC ant | sPVI + CFAE | A |
| 21 | 22 | 235 | LI post | LI ant | sPVI | A |
| 22 | 23 | 431 | RS top-pos | RI ant | cPVI + Roof/MI line | В |
| 23 | 24 | 235 | RI bot-post | RI bot-ant | sPVI + Roof line + CFAE | A |
| 24 | 25 | 214 | LS bot-post | LI bot | sPVI + Roof line + CFAE | С |
| 25 | 26 | 238 | RS bot-ant | RS top | sPVI | A |
| 26 | 27 | 210 | LS bot-post | LS bot-ant | sPVI + Roof line + CFAE | A |

Ant, anterior; AT-CL, atrial tachycardia-cycle length; Bot, bottom; CFAE, complex fractionated atrial electrogram; cPVI; circumferential pulmonary vein isolation; LC, left common; LI, left inferior; LS, left superior; MI, mitral isthmus; PV-gap, pulmonary vein-gap; RI, right inferior; RS, right superior; sPVI, segmental PVI.

Incidence of pulmonary vein-gap re-entrant atrial tachycardia following atrial fibrillation ablation

Atrial tachycardia due to proarrhythmia after prior PV isolation is not common; the previously reported incidence was 0.3-4%,^{5,7} additional linear ablation increases the incidence of AT to 20–48%.^{7,8} The main mechanism of AT after AF ablation is reported to be re-entry at the isthmus on the previous ablation lines, 80–90% of ATs following PV isolation were considered to be focal or localized re-entry related to the PV reconnection gap.9 Centrifugal activation pattern cannot always exclude re-entrant mechanism by itself, which can be recognized as the exit of the slow conduction isthmus in a re-entrant circuit on the PV gap, especially if the mapping resolution is insufficient. Gerstenfeld et al.² performed entrainment mapping in patients with focal AT following PV isolation, which revealed that most of these ATs were localized re-entry located at the PV ostium and were related to the previous ablation lesions. The other studies reported a series of cases of AT after circumferential PV isolation, in which approximately 30% of ATs were small-loop re-entrant AT related to PV isolation lesions,¹⁰ while 73% of ATs had a single localized site with narrow, low-amplitude, fractionated long-duration electrograms on the critical isthmus associated with the previous PV isolation lines.⁷ Since these studies assessed the mechanisms of AT after AF ablation using conventional 3D-EAM with limited low-density and low-resolution mapping, the detailed circuit of a small re-entry could not be determined. Satomi et al.4 elegantly presented a macroreentry circuit involving the LA, PV and two conduction gaps in previous lesions, and most ATs showing a focal pattern on 3D-EAM were diagnosed as PV-gap RAT by entrainment mapping. Consistently with other studies, they reported that most ATs related to PV gaps presented a focal pattern from the exit site of the PV, even on conventional 3D-EAM (CARTO or Navx); thus, cases could be misdiagnosed as classical focal AT without detailed entrainment mapping. In fact, in their study, the mean number of mapping points obtained using a 3.5-mm electrode tipped ablation catheter was 99 ± 7 ,⁴ thus, the resolution and density of mapping was quite limited. In the present study, we used a high-resolution mapping system with >15 000 mapping points. This made it possible to delineate the detailed circuit, even in the narrow areas like PVs. In fact, we demonstrated three localized re-entrant ATs (diameter, <3 cm) with a Type

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| | Type A (N = 16) | Туре В (<i>N</i> = 6) | Type C (<i>N</i> = 4) | P-value |
|--|-----------------|------------------------|------------------------|---------|
| AT-CL (ms) | 256 ± 48 | 276±76 | 239 ± 28 | 0.56 |
| PVI method (segmental/circumferential) | 14/2 | 0/6 | 4/0 | <0.01 |
| Prior linear line | 7 (44%) | 1 (17%) | 4 (100%) | 0.03 |
| Entrance gap | | | | |
| Width (mm) | 7.0 ± 2.2 | 8.9 ± 3.2 | 8.2 ± 1.7 | 0.23 |
| Voltage (mV) | 0.16 ± 0.11 | 0.12 ± 0.06 | 0.29 ± 0.24 | 0.10 |
| Signal duration (ms) | 87 ± 26 | 91 ± 33 | 73 ± 20 | 0.58 |
| Velocity (m/s) | 0.08 ± 0.05 | 0.30 ± 0.34 | 0.15 ± 0.07 | 0.07 |
| Exit gap | | | | |
| Width (mm) | 7.2 ± 1.9 | 11.1 ± 7.6 | 6.2 ± 1.2 | 0.08 |
| Voltage (mV) | 0.14 ± 0.08 | 0.32 ± 0.42 | 0.11 ± 0.02 | 0.16 |
| Signal duration (ms) | 79 ± 24 | 79 ± 31 | 69 ± 8 | 0.72 |
| Velocity (m/s) | 0.10 ± 0.07 | 0.15 ± 0.16 | 0.13 ± 0.09 | 0.50 |
| Conduction time of LA (ms) | 113 ± 66 | 128 ± 75 | 137 ± 34 | 0.75 |
| Conduction time within PV (ms) | 143 ± 60 | 148 ± 65 | 102 ± 56 | 0.45 |

AT-CL, atrial tachycardia-cycle length; LA, left atrium; PV, pulmonary vein; PV-gap RAT, PV-gap re-entrant atrial tachycardia; PVI, pulmonary vein isolation.



A circuit. Our data might suggest that the mechanism of classical focal AT and localized re-entrant AT associated with the previous PV isolation lesions could mostly be explained by PV-gap re-entry.

Re-entrant circuits of pulmonary veingap re-entrant atrial tachycardia

Previous studies demonstrated some cases of macro-reentrant AT conduction at two gaps on the previous PV isolation line ('PV-gap reentry') with and without the use of a conventional 3D-EAM system (CARTO or Navx).^{47,9} These re-entrant circuits were all located around the ipsilateral PVs through the two reconnected gaps (entrance and exit), and most of these cases had entrance and exit gaps in different PVs (Type B in this study). Only one study showed two gaps in the same PV (Type A in this study). In the present study, Type A and B circuits were observed in patients who underwent segmental and circumferential PV isolation, respectively. In addition, we also demonstrated PV-gap re-entry with a large circuit including the contralateral PVs (Type C circuit) for the first time. This type of circuit occurred due to the complete conduction block line through the roof and the mitral isthmus lines in the previous procedure. Thus, PV-gap RAT may occur whenever two PV gaps with incomplete lesions from the previous ablation are present, regardless of the PV isolation method (segmental or circumferential) and additional substrate ablation; the type of the circuit is variable and depends on the previous ablation procedure. In fact, PV-gap re-entrant AT after segmental and circumferential PV isolation was similarly identified in 9.8% and 8.2% in the entire population, respectively (P = 0.84).

Electroanatomical characteristics of pulmonary vein-gap re-entrant atrial tachycardia

The current study demonstrated two critical isthmuses on different PV-gaps during PV-gap RAT. As shown in previous studies, $^{\rm 11-13}$ the critical isthmus generally presents a lower voltage and slower conduction during re-entrant arrhythmias, and can be targeted for the ablation. Laţcu et al.14 recently demonstrated the detailed electrophysiological characteristics with a lower electrogram (EGM) amplitude and a significantly slower conduction velocity on the critical isthmus in comparison to the surrounding tissue during scar-related AT using an ultra-high-resolution mapping system (Rhythmia[™]). Our study showed similar results, with regard to the distinctive electrophysiological features of the critical isthmus including a narrow width, low amplitude with continuous fragmented signal and slow conduction. Moreover, the present study revealed a novel and interesting finding: PV-gap RATs had two critical isthmuses on the circuit, and usually presented similar electrophysiological features on both the entrance and exit gaps. Thus, the conduction time within the PV occupied more of the TCL (approximately 50% of the TCL) during AT. In addition, the critical isthmus was clearly identified by highresolution mapping; thus, Rhythmia^{TM}-guided ablation targeting the evident isthmus (entrance or exit gap) could be effective.

P-wave morphology of pulmonary veingap re-entrant atrial tachycardias

The presence of a discrete P-wave separated by an isoelectric interval in all leads has traditionally been regarded as a clue indicating focal AT.¹⁵ This can be explained by the fact that the isoelectric line usually reflects the absence of electric activity; that is, the atrial diastolic pause. Alternatively, the isoelectric interval may reflect a time interval when very low amplitude electric activity occurs. An isoelectric line may therefore result from slow conduction and/or the presence of scar tissue. The localized re-entry has an isthmus, which is recognized by low-amplitude, long-duration EGMs that usually cover approximately 50% or more of TCL; this relationship is close to that of the P-wave and the isoelectric line during focal AT.¹⁶ On the other hand, a discrete P-waves separated by an isoelectric interval are rarely observed in macro-reentrant AT because the atrial activated time occupies almost the whole TCL, except in cases showing an isthmus with very slow conduction or a large amount of atrial scar tissue. However, PV-gap RAT demonstrated a distinctive isoelectric interval in all leads in the current study, which is based on the fact that approximately 50% of the TCL time was spent within the PVs due to the presence of a double slow conduction zone (entrance and exit PV-gaps). In fact, there was a good correlation between the isoelectric duration and activation time within the PV (entrance-to-exit gaps). Thus, macro-reentry cannot be excluded, even when the presence of an apparent isoelectric line is observed on 12-lead ECG during AT.

P-wave polarity provides almost no help in differentiating between different AT mechanism or sites of origin. Only a negative P-wave in lead V1 can predict a right atrial origin.^{17,18} The P-wave is mostly influenced by the activation of bystander areas with voltage that is more preserved and which are distant from the AT circuit or focus. In fact, all cases showed a positive or RS pattern in lead V1; however,

the polarity of the P-wave in the peripheral lead was variable in the present study.

Limitations

First, although this multicentre study included six high-volume centres, the number of cases with PV-gap AT was relatively small. Further studies are needed to clarify the electroanatomical and ECG features of these ATs. Second, in this population six patients were taking amiodarone before the ablation procedure, and AT-CL was tend to be longer in patients taking amiodarone compared with those without $(313 \pm 81 \text{ vs. } 242 \pm 27 \text{ ms}, P = 0.08)$. However, there was no significant difference statistically in the width, signal duration/voltage, and velocity on the gap between patients with/without amiodarone. The influence of amiodarone seems to be small but it might affect the results. Last, although it is difficult to precisely define whether the PV gap sites were located on the previous pulmonary vein isolation lines. all PVs associated with PV-gap re-entry were successfully isolated during the index procedure, therefore, two gaps between PVs and the LA need to be identified based on the fact that the re-entrant circuit included the PVs. In this respect, two electrically slow conduction sites between PV and the LA were defined as the gaps on the estimated previous ablation line.

Conclusions

The novel ultra-high-resolution mapping system revealed the PV-gap RAT circuit in detail, and showed two gaps (entrance and exit) with distinctive electrophysiological features. The PV-gap RAT circuits were variable, and included macro- and localized re-entry that was associated with the previous ablation lesions. These could be simply and curatively treated with catheter ablation targeting the entrance or exit PV-gap with a guidance of this high-resolution mapping system.

Supplementary material

Supplementary material is available at Europace online.

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5-4. Characteristics of Single-Loop Macroreentrant Biatrial Tachycardia Diagnosed by Ultrahigh- Resolution Mapping System

1463

1464 Background and purpose of the study

- 1465 In this study, we would like to focus on the characteristics of a rare type of complex ATs, 'single-loop macroreentrant 1466 biatrial tachycardia' diagnosed with the RhythmiaTM. Biatrial tachycardia (BiAT) is a rare form of AT using 2
- 1467 interatrial bridges and 2 atrias, which is reported to be observed in patients with a history of open heart surgery^{94,95},
- 1468 corrected congenital heart disease⁹⁶, or atrial fibrillation (AF) ablation⁹⁷. We tried to systematically assess the circuit
- 1469 and mechanism of these ATs.

1470 Methods and results

- 1471 We identified 8 (2.4%) patients with 9 (2.1%) BiATs in a cohort of 336 consecutive patients with 422 mapped ATs
- 1472 from 2 institutions who had undergone AT CA using the RhythmiaTMn mapping system as described in the **Figure 5**-
- 1473 **4 and Table 5-4.** Seven of the 8 patients had a history of persistent AF ablation, including septal or anterior left
- 1474 atrium ablation before developing BiAT. One of the 8 patients had a history of an atrial septal patch closure with a
- 1475 massively enlarged right atrium.
- 1476 We observed 3 types of BiAT as shown in the **Figure 5-4**: (1) BiAT with a perimitral and peritricuspid reentrant 1477 circuit (n=3), (2) BiAT using the right atrium septum and a perimitral circuit (n=3), and (3) BiAT using only the left
- 1478 atrium and right atrium septum (n=3).



Figure 5-4. Simplified schema of 3 types of biatrial AT

Type 1 BiAT was defined as an AT with a reentrant circuit using most of mitral annulus in the LA circuit (including the coronary sinus (CS) but excluding the LA septum) and most of the tricuspid annulus in the RA circuit (excluding the RA septum) with 2 interatrial connections. Type 2 BiAT was defined as an AT with a reentrant circuit using most of mitral annulus in the LA circuit (including the CS but not the LA septum) and the RA septum with 2 interatrial connections. Type 3 BiAT was defined as an AT with a reentrant circuit using LA septum with 2 interatrial connections.

1493

| | | Initial Diagnosis | Initial Ablation Strategy | Index PVI | Index Roof | Index MI | Index LA Septum | Index LA Anterior | Index Anterior Line | Index CTI | Rhythm at the Beginning | AT Induction Mode |
|--------|---------------------|----------------------|---------------------------------|------------|---------------|-------------------|--------------------|----------------------|---------------------------|------------|-------------------------------|---|
| | Patient 1, BiAT1 | PsAF | ECGi | + | + | - | + | + | - | + | Sinus | Pacing |
| Type A | Patient 2, BiAT2 | PsAF | Defrag | + | + | + (incomplete) | + | + | - | + | Sinus | Pacing |
| | Patient 3, BiAT3 | PsAF | ECGi | + | + | + (incomplete) | + | + | - | + | Sinus | Pacing |
| | Patient 4, BiAT4 | PsAF | ECGi | + | + | - | + | + | - | + | AF | Pacing |
| Type B | Patient 5, BiAT5 | PsAF | PVI | + | - | - | - | - | - | - | AT | Spontaneously induced |
| | Patient 6, BiAT6 | PsAF | Defrag | + | - | - | + | + | + | + | AT | Converted from BiAT7 |
| | Patient 6, BiAT7 | PsAF | Defrag | + | - | - | + | + | - | + | AT | On arrival in catheter laboratory |
| Type C | Patient 7, BiAT8 | PsAF | ECGi | + | + | - | + | + | - | + | Sinus | Converted from the other AT |
| | Patient 8, BiAT9 | tAFL | СТІ | - | - | - | - | - | - | + | Sinus | Converted from the other AT |
| | | PsAF 88.9% | | 8/9, 87.5% | 4/9, 44.4 | 2/9, 22.2% | 7/9, 77.7% | 7/9, 77.7% | 1/9, 11.1% | 8/9, 87.5% | | |

1494

1495 Table 5-4. Background Information of Each Biatrial Tachycardia

1496

CA successfully terminated 8 of the 9 BiATs (the remaining 1 AT mechanically terminated on the circuit). Complete understanding of the AT circuit allowed identification of the appropriate target in most patients. In circuits dependent on an AV valve annulus, that is, types 1 and 2, the preferred target is a classic anatomic isthmus (CTI or MI line). In type 3, septal lesions can be more challenging because of the risk of AV block possibly resulting from direct AV node ablation. Thus, a minimal line or point ablation may be safer. For all types, when delivering RF energy for septal or interatrial connections, it should be realized that this may lead to more extensive intra-atrial conduction delay or AV block (possibly because of the direct effect on the compact AV node).

1504 Summary and conclusion

We demonstrated that: (1)Although BiAT infrequently occurs in 2% of AT patients, this AT should be considered in the patients with BiAT having an electric obstacle located in the septum, with understanding of the circuits. (2)By using the high-resolution mapping system, 3 types of BiATs are identified depending on the characteristics of the circuit.

In conclusion, all patients who developed BiAT had an electric obstacle on the septum, most commonly with prior anteroseptal LA ablation. In patients with this type of previous ablation, mapping of both atria should be considered during mapping of MAT. Because 3 types of single-loop BiATs were observed, ablation strategies should be adjusted to the type of BiAT circuit.

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- 1516 10.1161/CIRCEP.117.005558.

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- 1518 Characteristics of Single-Loop Macroreentrant Biatrial Tachycardia Diagnosed by Ultrahigh-Resolution
- 1519 Mapping System.
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1523

ORIGINAL ARTICLE

Characteristics of Single-Loop Macroreentrant Biatrial Tachycardia Diagnosed by Ultrahigh-Resolution Mapping System

BACKGROUND: Biatrial tachycardia (BiAT) is a rare form of atrial macroreentrant tachycardia, in which both atria form a critical part of the circuit. We aimed to identify the characteristics and precise circuits of single-loop macroreentrant BiATs.

METHODS AND RESULTS: We identified 8 patients (median age, 59.5 years old) with 9 BiATs in a cohort of 336 consecutive patients from 2 institutions who had undergone AT catheter ablation using an automatic ultrahigh-resolution mapping system. Seven of the 8 patients had a history of persistent AF ablation, including septal or anterior left atrium ablation before developing BiAT. One of the 8 patients had a history of an atrial septal patch closure with a massively enlarged right atrium. Nine ATs (median cycle length, 334 ms; median 12 561 points in the left atrium; 8814 points in the right atrium) were diagnosed as single-loop macroreentrant BiATs. We observed 3 types of BiAT (1) BiAT with a perimitral and perimitral circuit (n=3), (2) BiAT using the right atrium septum and a perimitral circuit (n=3). Catheter ablation successfully terminated 8 of the 9 BiATs.

CONCLUSIONS: All patients who developed BiAT had an electric obstacle on the anteroseptal left atrium, primarily from prior ablation lesions. In this situation, mapping of both atria should be considered during AT. Because 3 types of single-loop BiAT were observed, ablation strategies should be adjusted to the type of BiAT circuit. Takeshi Kitamura, MD et al

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Key Words: atrial fibrillation atrial septum atrial tachycardia catheter ablation ultrahighresolution mapping

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WHAT IS KNOWN?

- Biatrial tachycardia (BiAT) is a rare form of atrial macroreentrant tachycardia.
- BiAT is often observed in patients with a history of open heart surgery, corrected congenital heart disease, or atrial fibrillation ablation.

WHAT THE STUDY ADDS?

- All the patients with BiAT had an electric obstacle located in the septum, which was considered to be the critical component supporting BiAT.
- There were 3 types of BiATs classified by the characteristics of the circuit with the detailed evaluation.

Biatrial tachycardia (BiAT) is a rare form of atrial tachyarrhythmia using 2 interatrial bridges and 2 atria, which is most often observed in patients with a history of open heart surgery,^{1,2} corrected congenital heart disease,³ or atrial fibrillation (AF) ablation.⁴ Several case reports¹⁻⁴ with activation maps of BiAT from 3-dimensional (3D) mapping systems have been described, but only 1 detailed mapped case series was reported with a 3D mapping system.⁴ Thus, the full particulars of BiAT may not have been previously identified. In the present study, we assessed the characteristics and precise circuit of BiAT by using an ultrahigh-density mapping system.

METHODS

The data, analytic methods, and study materials will be/ have been made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

In a consecutive series of patients who underwent AT ablation using an automatic high-density mapping system in 2 institutions (Bordeaux and Toulouse) from November 2014 to March 2017, all patients with BiAT were analyzed. In each case, we evaluated the precise circuits in both the left atrium (LA) and right atrium (RA) during BiAT on the high-density activation map. Written informed consent was obtained from all patients. Our institution's research ethics board approved this study.

Ablation Procedure

Catheter ablation for AT was performed under mild sedation using midazolam and morphine; oral anticoagulation was continued in the patients receiving vitamin K antagonists; in patients with novel oral anticoagulants, they were withheld

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Kitamura et al; Single-Loop Biatrial Tachycardia

for at least 1 day before ablation. Antiarrhythmic drugs were discontinued >5 half-lives before ablation with the exception of amiodarone. In all patients, transesophageal echocardiography or an enhanced computed tomographic scan was performed before the procedure to exclude intracardiac thrombus. During the procedure, intracardiac electrograms were continuously recorded and stored at a sweep speed of 100 mm/s on a computer-based digital system (Labsystem Pro, BARD, Boston Scientific, MA). After placement of a deflectable decapolar catheter within the coronary sinus (CS) (Extreme, Sorin/Dynamic XT, Boston Scientific, MA), a transseptal puncture was performed under fluoroscopic guidance; 1 transseptal sheath (Agilis NxT steerable sheath, St Jude Medical) was introduced into the LA. Systemic anticoagulation with a heparin bolus (target activated clotting time >300 s) was performed. Before inserting the mapping multipolar catheter, heparin (100/IU/kg) was administered to achieve an activated clotting time of >300 s. Subsequent boluses of heparin were administered every 20 to 30 minutes if needed. Electroanatomical navigation was performed using the Rhythmia mapping system. During the catheter ablation procedure, a 3.5-mm tip open-irrigated catheter (ThermoCool SF, Biosense Webster, Diamond Bar, CA) was used. Maximum RF energy delivery was set at 30 to 40 W with a temperature limit of 45°C; irrigation was set at 10 to 15 mL/min.

Ultrahigh-Resolution Electroanatomical Mapping

The Rhythmia mapping system (Boston Scientific, MA) uses a 64-pole mini-basket mapping catheter (Orion; Boston Scientific, MA), which incorporates small unidirectional electrodes (0.4 mm²; 2.5 mm spacing) to suppress far-field signals. Detailed electroanatomical mapping of the LA and RA was performed using bidirectional flexion with the basket in variable degrees of deployment (diameter ranging from 3 to 22 mm). The reference electrogram was selected on the decapolar catheter and placed in the CS. An activation map was created under the standard beat acceptance criteria (automatic): (1) cycle length (CL) variation <10 ms, (2) <5 ms activation time difference variations between the CS electrograms, (3) catheter motion <1.0 mm per beat, and (4) catheter tracking uncertainty <3 mm. For fragmented or multiple potential electrocardiogram, the system takes into account the timing in the surrounding area to select the potential to use for timing annotation. In the case of a lack of statistical coherence between neighboring points in an area, no color code is displayed (the area is left gray). Selection of the surface electrocardiogram is based on the projection distance (standard setting was 2 mm): only electrocardiograms recorded within the projection distance from the surface geometry are displayed. After map completion, dense scar thresholding was performed wherever necessary to visualize the entire circuit. The confidence mask parameter was finely tuned for each map and lowered as much as needed for each AT. The confidence mask was nominally established as 0.03 mV.

Diagnosis for BiAT

Activation maps in both LA and RA were studied for each BiAT. A single-loop macroreentrant BiAT was diagnosed if

the propagation revealed a reentrant circuit using the LA and RA by a single-loop and RF application on the circuit terminated the BiAT, or preferably, entrainment at points throughout the circuit was followed by a postpacing interval <20 ms greater than the tachycardia CL.

We then classified BiATs into 3 groups according to the circuit, type 1: BiAT using most of the mitral annulus in the LA circuit (including the CS but not the LA septum) and most of the tricuspid annulus in the RA circuit, apart from the RA septum, with 2 interatrial connections (Figure 1; upper); type 2: BiAT using most of the mitral annulus in the LA circuit (including CS) and the RA septum with 2 interatrial connections (Figure 1; upper middle); type 3: BiAT using the LA septum and RA septum with 2 interatrial connections (Figure 1; lower middle). We analyzed the characteristics of all BiATs and the 3 types of BiATs.

Ablation Target and Outcome

Based on the activation map, the narrowest isthmus of the BiAT circuit was chosen as the primary target, and a linear lesion was created across the isthmus connecting scars and anatomic obstacles. Termination of BiAT to sinus rhythm or to another AT during RF application was defined as an AT termination. Noninducibility of the tachycardia after ablation was also defined as an acute success. AT induction was performed by incremental burst pacing to a minimum pacing CL of 200 ms or the local effective refractory period of atrial tissue.

Follow-Up

Patients were followed for clinical and asymptomatic recurrences. All patients had regular visits to the referring cardiologist 1, 3, 6, and 12 months after the ablation procedure with a 12-lead ECG and 24-hour Holter monitoring.

Statistics

Continuous variables are summarized by median±interquartile range (25th–75th percentile). Comparison of continuous variables among 3 groups was performed using the Kruskal– Wallis test. Subsequently, Dunn test was used for post hoc analysis between each group after Kruskal–Wallis test. All reported *P* values are 2-sided, with a *P* value of <0.05 considered to indicate statistical significance. Statistical analyses were performed using the Statistical Package for Social Studies, version 24.0 (IBM, Armonk, NY).

RESULTS

Patient Population

In a series of 336 consecutive patients (median age, 59.5 [50.8–69.3] years old) who underwent AT ablation with the Rhythmia system from November 2014 to March 2017 in 2 institutions (Bordeaux and Toulouse), a total of 422 ATs were mapped. Of those, 9 BiATs (9/422, 2.1%) in 8 patients were identified. Of the 265 patients with AT who initially underwent ablation for persistent AF, 7 patients (patients No. 1–7) developed

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Figure 1. Simplified schema of 3 types of biatrial tachycardia (BiAT) reentrant circuit.

The circuit of each type of BiAT is demonstrated in each panel with median activation duration of the circuit in each chamber and percentages of tachycardia cycle length (TCL) in each chamber. Upper, Type 1 BiAT was defined as an AT with a reentrant circuit using most of mitral annulus in the left atrium (LA) circuit (including the coronary sinus [CS] but excluding the LA septum) and most of the tricuspid annulus in the right atrium (RA) circuit (excluding the RA septum) with 2 interatrial connections. Middle, Type 2 BiAT was defined as an AT with a reentrant circuit using most of mitral annulus in the LA circuit (including the CS but not the LA septum) and the RA septum with 2 interatrial connections. Lower, Type 3 BiAT was defined as an AT with a reentrant circuit using LA septum and RA septum with 2 interatrial connections. As shown below, the dashed line, the black line between both atria shows the fossa ovalis as an insulator. A black colored broad bar at septum indicates a massive, substantial electric obstacle. A gray hatched bar indicates a partial electric obstacle.

BiAT (2.6%, 7/265). The other patient (patient No. 8) had a history of atrial septal patch closure for an atrial septal defect with an enlarged RA because of Eisen-

Table 1. Patients Characteristics

| Variables (N=8) | |
|---|------------------|
| Age, y | 59.5 (50.8-69.3) |
| Male/female sex, n | 7/1 |
| CHA2DS2-VASc score | 1.0 (1.0–3.0) |
| Index procedure numbers | 2.0 (2.0-3.0) |
| Initial diagnosis of persistent atrial fibrillation | 7/8 (87.5%) |
| Left ventricular ejection fraction, % | 59.9 (58–65.6) |
| Total procedure time, min | 245 (240-375) |
| Median follow-up period, mo | 12.4 (9.3–20.0) |
| Recurrence of atrial tachyarrhythmia, n (%) | 1/7 (14.2%) |

menger syndrome. Patient characteristics are shown in Table 1. The median number of prior procedures was 2.0 (2–3). Only 1 patient (patient No. 2) had left ventricular systolic dysfunction with a left ventricular ejection fraction of 30%.

Index Ablation Lesions

Only 1 patient had an index procedure limited to pulmonary vein isolation, whereas 6 of the 7 patients with persistent AF had an extensive index procedure with substrate ablation beyond pulmonary vein isolation (Table 2). The remaining patient (patient No. 8) with atrial septal defect patch closure had a history of previous cavotricuspid isthmus linear ablation.

AT Diagnosis

The characteristics of BiATs are shown in Figure 1 and Tables 2 and 3. All of the ECGs of the BiATs are shown in Figure 2. A total of 9 BiATs with high-density maps were observed (Table 3). The median CL was 334 ms (296–406, range, 250–450 ms). All ATs used the right and left atria as a part of the single-loop reentrant circuit. The median activation duration in the LA circuit was 210 (182–226) ms, which was 57.8 (54.5–67.1)% of the tachycardia CL. The median activation duration in the RA circuit was 122 (119–180) ms, which was 42.2 (32.9–45.5)% of the tachycardia CL.

There were 3 BiATs (Table 4) classified as type 1 (BiAT 1–3; Figure 3), 3 BiATs classified as type 2 (BiAT 4–6; Figure 4), and 3 BiATs classified as type 3 (BiAT 7–9; Figure 5). The maps of the remaining BiATs are presented as supplemental files (Figure 1 through VI in the Data Supplement).

Interatrial Conduction

The earliest activation site in the RA was the high-mid septum among the 7 BiATs with counter clockwise rotation (BiAT 1–7, 7/7: 100%), whereas in LA, it was the inferior aspect close to the CS ostium in 6 BiATs (BiAT

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| | Initial Diagnosis | Initial Ablation Strategy | Index PVI | Index Roof | Index MI | Index LA Septum | Index LA Anterior | Index Anterior Line | Index CTI | Rhythm at the Beginning | AT Induction Mode |
|---------------------|----------------------|---------------------------------|------------|---------------|-------------------|--------------------|----------------------|---------------------------|------------|-------------------------------|---|
| Patient 1, BiAT1 | PsAF | ECGi | + | + | - | + | + | - | + | Sinus | Pacing |
| Patient 2, BiAT2 | PsAF | Defrag | + | + | + (incomplete) | + | + | - | + | Sinus | Pacing |
| Patient 3, BiAT3 | PsAF | ECGi | + | + | + (incomplete) | + | + | - | + | Sinus | Pacing |
| Patient 4, BiAT4 | PsAF | ECGi | + | + | - | + | + | | + | AF | Pacing |
| Patient 5, BiAT5 | PsAF | PVI | + | - | - | - | - 1 | - | - | AT | Spontaneously induced |
| Patient 6, BiAT6 | PsAF | Defrag | + | - | - | + | + | + | + | AT | Converted from BiAT7 |
| Patient 6, BiAT7 | PsAF | Defrag | + | - | - | + | + | - | + | AT | On arrival in catheter laboratory |
| Patient 7, BiAT8 | PsAF | ECGi | + | + | - | + | + | - | + | Sinus | Converted from the other AT |
| Patient 8, BiAT9 | tAFL | СТІ | - | | - | - | | - | + | Sinus | Converted from the other AT |
| | PsAF 88.9% | | 8/9, 87.5% | 4/9, 44.4 | 2/9, 22.2% | 7/9, 77.7% | 7/9, 77.7% | 1/9, 11.1% | 8/9, 87.5% | | |

Table 2. Background Information of Each Biatrial Tachycardia

AF indicates atrial fibrillation; ASD, atrial septal defect; AT, atrial tachycardia; BiAT, biatrial tachycardia; CTI, cavotricuspid isthmus; defrag, defragmentation of LA guided by local signals; ECGi, noninvasive body surface mapping guided ablation; LA, left atrium; MI, mitral isthmus; NA, not accessed; PsAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; RA, right atrium; and tAFL, typical atrial flutter.

1–6, 6/7: 85.7%) and the higher anterior area in BiAT 7 (1/7, 14.3%). However, among the BiATs with clockwise rotation (BiAT 8 and 9), the earliest site was close to the anterior-mid septum in the RA, and the high septum was close to the roof in the LA. Six of 8 BiATs were terminated targeting the isthmus identified by the activation map (cavotricuspid isthmus in BiAT 1 and 2; the isthmus between an anteroseptal LA scar and the mitral valve in BiAT 5, 7 and 8; an isthmus between the atrial septal defect patch scar and the superior vena cava in RA BiAT 9). The remaining BiAT were terminated by targeting interatrial connection at the high RA septum (BiAT 4 and 6). After ablation, noninducibility was verified in 7 of 8 cases (87.5%). In patient No. 7, induction was not performed at the end of the procedure.

Ablation Result

In 7 of 8 cases (patients No. 1, No. 2, No. 4–8), 8 BiATs (88.9%) were successfully terminated by RF application.



Figure 2. Twelve-lead electrocardiographs of all biatrial tachycardias (BiAT) by 50 mm/sec, 0.25 mV (arranged to see atrial activity clearly).

The P wave morphologies had wide variations, and the atrial activity in BiAT 2, 3, and 8 was unclear.

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| | AT CL, ms | LA Number of Mapping Points | LA Mapping Time, s | LA Activation Time, (ms: % of Total CL) | RA Number of Mapping Points | RA Mapping Time, s | RA Activation Time, (ms: % of Total CL) | CS Sequence | AT Termination, or Change by Ablation | AT Termination Site | No Inducibility at the End of Procedure |
|---------------------|------------------|-----------------------------------|--------------------------|---|-----------------------------------|--------------------------|---|-----------------------|--|---------------------------|---|
| Patient 1, BiAT1 | 334 | 11624 | 563 | 182 (54.6%) | 20891 | 580 | 152 (45.5%) | Prox-Dist | Termination | СТІ | + |
| Patient 2, BiAT2 | 415 | 12561 | 907 | 210 (50.6%) | 4045 | 332 | 205 (49.4%) | Prox-Dist | Termination | СТІ | + |
| Patient 3, BiAT3 | 450 | 16805 | 1029 | 260 (57.8%) | 1783 | 178 | 190 (42.2%) | Prox-Dist | Mechanical | N/A | + |
| Patient 4, BiAT4 | 388 | 17775 | 1090 | 269 (69.3%) | 10531 | 574 | 119 (30.7%) | Prox-Dist | Change to AT | High septum at RA | + |
| Patient 5, BiAT5 | 296 | 10313 | 898 | 214 (72.3%) | 3789 | 280 | 82 (27.7%) | Prox-Dist | Termination | LA anterior | + |
| Patient 6, BiAT6 | 307 | 19954 | 861 | 206 (67.1%) | 8814 | 719 | 101 (32.9%) | Prox-Dist | Termination | High septum at RA | + |
| Patient 6, BiAT7 | 296 | 7551 | 2143 | 174 (58.8%) | 12290 | 583 | 122 (41.2%) | Prox-Dist | Change to AT | LA anterior | + |
| Patient 7, BiAT8 | 406 | 14177 | 756 | 226 (55.7%) | 2516 | 190 | 180 (44.3%) | Prox-Dist | Termination | LA anterior | Not assessed |
| Patient 8, BiAT9 | 250 | 7366 | 552 | 128 (51.2%) | 11715 | 362 | 122 (48.8%) | Dist-Prox | Change to AT | RA septum | + |
| | 334 (296–406) | 12561 (10313–16805) | 898 (756–1029) | 210 (182–226), (57.8% [54.5–67.1]) | 8814 (3789–11715) | 362 (280–580) | 122 (119–180), (42.2% [32.9–45.5]) | Prox–Dist, (88.8%) | 8/9, (88.8%) | | 8/9, (88.8%) |

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AT indicates atrial tachycardia; BiAT, biatrial tachycardia; CL, cycle length; CS, coronary sinus; CTI, cavotricuspid isthmus; Dist, distal; LA, left atrium; MI, mitral isthmus: Prox. proximal: and RA. right atrium.

Follow-Up

During a median follow-up period of 12.4 (9.3-20) months, there was 1 recurrence in patient No. 5 (12.5%, 1/8).

DISCUSSION

- The main findings of our study are as follows:
 - 1. We observed that all the patients with BiAT had an electric obstacle located in the septum, which

| Table 4. | Comparison of 3 | 3 Types | of Biatrial | Tachycardia |
|----------|-----------------|---------|-------------|-------------|

| | Type 1 (n=3, BiAT1–3) | Type 2 (n=3, BiAT4–6) | Type 3 (n=3, BiAT7–9) | P Value |
|---|-----------------------------|-----------------------------|-----------------------------|------------|
| Median AT CL, ms | 415 (375–433) | 307 (302–348) | 296 (273–351) | 0.184 |
| Median LA activation time on the circuit, ms | 210 (196–235) | 214 (210–242) | 174 (151–200) | 0.393 |
| Median percentage of LA activation time (% of total CL) | 54.5 (52.6–56.1) | 69.3 (68.2–70.8) | 55.7 (53.4–57.2) | 0.061 |
| Median RA activation time on the circuit, ms | 190 (171–198)* | 101 (92–110)* | 122 (122–151) | 0.038† |
| Median percentage of RA activation time (% of total CL) | 45.5 (43.9–47.5) | 30.7 (29.2–31.8) | 44.3 (42.8–46.6) | 0.061 |

AT indicates atrial tachycardia; CL, cycle length; LA, left atrium; and RA,

right atrium.

*P<0.05 by post hoc Dunn test. +P<0.05 by Kruskal–Wallis test.

was considered to be the critical component supporting BiAT.

2. We have, by using high-density mapping, identified 3 types of BiATs classified by the characteristics of the circuit.

Prevalence of Patients With BiAT

Single-loop macroreentrant BiAT is a rare form of macroreentrant AT, first described in 1998.1-6 In 2015, Mikhaylov et al4 identified 4 patients with BiAT in a cohort of 807 patients who underwent AF ablation guided by a 3D mapping system (4/807, 0.5%). In the present study, we observed 8 patients (2.3%; 8/341 patients) with 9 BiATs (2.1%; 9/422 tachycardias), which was 2.7% (7/263) among patients with prior AF ablation.

Mechanism and Circuits of Single-Loop Macroreentrant BiAT

As has been described in previous reports, BiAT is dependent on an obstacle to conduction in the LA septum.²⁻⁴ Prior AF ablation is the commonest cause of such an obstacle in the present study. Mapping of activation in both atria is indicated, therefore, in AT where there is a history of extensive AF ablation or the presence of an anatomic obstacle to conduction. In most present cases, BiAT was considered in the differential diagnosis when there was a history of significant septal anterior

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Figure 3. High-density activation maps and voltage map during biatrial tachycardia (BiAT) 1, and intracardiac electrogram at termination of BiAT1 during radiofrequency application.

A, BiAT1 had a tachycardia cycle length of 334 ms with counterclockwise rotation. Propagation ran around the mitral valve from coronary sinus (CS) ostium to the anterior part of the left atrium (LA) beneath the left atrial appendage, then along the LA anterior wall to the septum, from where propagation jumped to the right atrium (RA). Examination of both atrial maps revealed a single-loop macroreentrant circuit using part of mitral annulus and tricuspid annulus. Entrainment pacing from cavotricuspid isthmus (CTI), CS ostium, and CS distal part showed postpacing interval (PPI)-tachycardia cycle length (TCL) of 0 ms, therefore, both atrioventricular (AV) valve annuli were involved in the circuit, making this type 1 BiAT. B, Posteroanterior (PA) view demonstrating that propagation from inferior to posterior was blocked by posterior scar. C. Inferior view demonstrating that propagation from anterior to inferior was blocked by inferior scar. D, On the RA map, activation passed from the high posterior septum toward the anterior free wall and then down along the tricuspid valve through the cavotricuspid isthmus (CTI) to the CS and then the LA. In the right septum, there was wavefront collision between propagation from the CTI and the high septum. E, Successful ablation site and intracardiac electrograms at termination during radiofrequency application. F, Voltage maps during BiAT1 from anteroposterior (AP) view and posteroanterior (PA) view. Both pairs of pulmonary veins are isolated. A massive low voltage area (definition 0.5-0.05 mV) was observed at the posterior wall and anteroseptal wall. That area was thought to be a consequence of past ablation lesions and was considered to be an electric obstacle forcing the propagation to jump into the RA. IVC indicates inferior vena cava; LAO, left anterior oblique; LPO, left posterior oblique; RPV, right pulmonary vein; and SVC, superior vena cava.

ablation and an activation map could not identify a complete AT circuit in a single chamber. Entrainment pacing at the beginning of procedure may be helpful to clarify the involvement of both atria, at the risk of terminating the AT.

The use of high-density mapping in the present study has allowed us to define the course of the activation wavefront and thereby classify BiAT into 3 groups. Activation in each chamber proceeds either around the atrioventricular (AV) valve or via the septum; we identified 3 types. Type 1: BiAT with a reentrant circuit around the mitral and tricuspid annuli, using 2 interatrial connections without the septa being involved in the critical circuit. Propagation on both septa showed either collision or block. Type 2: BiAT with a reentrant circuit around the mitral

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Figure 4. High-density activation mapping of biatrial tachycardia (BiAT) 6.

A, BiAT 6 had a tachycardia cycle length (TCL) of 307 ms with counterclockwise rotation and was observed after RF ablation of BiAT 7. The course of propagation ran around a perimitral circuit from the coronary sinus (CS) ostium to left atrium (LA) anterior wall or LA septum. Then the propagation is passed to the right atrium (RA) from the LA high septum. RA propagation arose from the RA high septum. Then propagated from high to low in the RA septum and returned to the CS ostium. Entrainment pacing from earliest RA site on the high septum, RA mid septum, CS ostium, distal CS, and the high LA septum resulted in a postpacing interval (PPI) minus TCL of <20 ms. Therefore, BiAT 5 was type 2 BiAT. **B** and **C**, BiAT 5 was terminated during radiofrequency application at the earliest RA site on the high RA septum. AP indicates anteroposterior; and LAO, left anterior oblique.

annulus and the RA septum with wavefront collision or block in the LA septum. This is, to the best of our knowledge, the first description of each septum propagating separately, with conduction on one side and conduction block on the other. Type 3: BiAT with a reentrant circuit ran around the LA septum and RA septum, with passive activation around both AV valves. We did not observe activation around the tricuspid annulus and LA septum, without RA septal involvement, but such a circuit may, theoretically, be possible as type 4. Classification of BiAT in this manner highlights the importance of prior linear lesions in the maintenance of these tachycardias. All except type 3 are dependent on conduction in the mitral or tricuspid isthmuses and, therefore, on gaps in lines of block, should these have been ablated previously.

Finally, in terms of surface ECG analysis, the ECGs of BiAT 2, 3, and 8, identified atrial activities of low amplitude, which probably reflected a certain amount of damaged tissue in both atria. In addition, it is known that interpretation of the surface ECG post–LA ablation has major limitations that hinder its use.⁷ At this time, we think it is challenging to diagnose BiAT based on the surface ECG characteristics.

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Figure 5. High-density activation mapping of biatrial tachycardia (BiAT) 7.

BiAT 7 had a tachycardia cycle length (TCL) 296 ms with counterclockwise (CCW) rotation. The propagation of BiAT 7 circuit ran from the left atrium (LA) septum, with an interatrial conduction at the high septum, down the right atrium (RA) septum to an interatrial conduction to the LA septum with CCW rotation. Entrainment at LA low anterior septum revealed postpacing interval (PPI)–TCL by 16 ms. Entrainment at RA mid septum revealed postpacing interval (PPI)–TCL by 6 ms. Entrainment at mitral isthmus area showed a PPI–TCL of 55 ms. There were clear double potentials linearly located along with the LA septum reaching to isolated RSPV, which refrained from completing reentrant circuit in LA (marked as black small circles on the figure). Wavefront collision was observed at 12 o' clock on the mitral annulus. Therefore, BiAT 6 used both septa and was classified as type 3 BiAT. RF application at LA low anterior septum terminated BiAT 7, converting it to BiAT 6.

Electric Interatrial Connection

BiAT are dependent on there being 2 separate interatrial electric connections, ¹⁻⁴ as seen in all patients in the present study, despite extensive prior ablation. In keeping with previously described details of interatrial connection, ⁸⁻¹⁶ interatrial connection via Bachmann's bundle was intact in all cases in our series. The other limb of the circuit was the CS (7/9, 77.8%) or anterior septum (2/9, 22.2%). Interatrial connections are anatomically robust, with complex insertions over a wide area and epicardial connections, ¹²⁻¹⁷ which may explain the persistence of such connections despite widespread ablation and the difficulty in achieving interatrial connections an unattractive target for ablation of BiAT, and ablation at a critical isthmus distant to the interatrial connection may have greater success.

Where Is the First Ablation Target?

Complete understanding of the AT circuit allowed identification of the appropriate target in most patients. In circuits dependent on an AV valve annulus, that is, types 1 and 2, the preferred target is a classic anatomic isthmus (cavotricuspid isthmus or mitral isthmus line). In type 3, septal lesions can be more challenging because of the risk of AV block possibly resulting from direct AV node ablation. Thus, a minimal line or point ablation may be safer. For all types, when delivering RF energy for septal or interatrial connections, it should be realized that this may lead to more extensive intra-atrial conduction delay or AV block (possibly because of the direct effect on the compact AV node). In addition, in type 1 or type 2 BiAT, conduction delay to left atrial appendage may occur, but the electric connection via Bachmann bundle will still be preserved.

Study Limitations

In this case series, entrainment in both atria was not performed in all BiATs. However, mapping of each of the atria separately did not identify a reentrant circuit, and parts of the CL were missing in each chamber. In

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addition, other possible types of biatrial circuits may be possible-for example, BiAT using the tricuspid annulus and the LA septum (the missing type 4) or any subtypes of type 1 or type 2, such as those using the vein of Marshall or the carina of the left pulmonary veins. We used the Rhythmia system in the present study to provide case series with uniform mapping; however, we think it would be entirely possible to diagnose 3 types of BiAT if a sufficient number of mapping points were correctly annotated using any mapping system. Furthermore, even using a highdensity mapping system with a mini-basket multipolar catheter, we may have annotated far-field signals from the opposite septum when mapping either septum. In addition, the follow-up period was relatively short to determine the long-term efficacy of our ablation strategy for BiAT. Finally, the number of patients is still limited.

CONCLUSIONS

All patients who developed BiAT had an electric obstacle on the septum, most commonly with prior anteroseptal LA ablation. In patients with this type of previous ablation, mapping of both atria should be considered during mapping of macroreentrant AT. Because 3 types of single-loop BiATs were observed, ablation strategies should be adjusted to the type of BiAT circuit.

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FOOTNOTES

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^{14.} Lu'dinghausen VM, Ohmachi N, Boot C. Myocardial coverage of the coro-

1536 5-5. The role of Marshall bundle epicardial connections in atrial tachycardias after atrial 1537 fibrillation ablation

1538

1539 **Background and purpose of the study**

- 1540 The Marshall bundle (MB) has been reported to have variable connections to the adjacent myocardium⁹⁸. Patients
- 1541 who have more than 2 connections between the MB and the myocardium of the CS, LA or PVs have the anatomical
- substrate to generate localized reentry circuits or MATs around the MI, using the epicardial MB^{99,100}. Macroreentry
- 1543 using the MB has recently been reported in case series¹⁰¹, but localized reentry circuits using the MB post AF
- ablation have not been evaluated. We have focused on the MB-dependent ATs presenting after AF ablation, using
- 1545 the high-resolution mapping system, RhythmiaTM, to elucidate the mechanism of these ATs.

1546 Methods and Results

- 1547 A total of 199 ATs as shown in the Figure 5-5 were mapped in 140 patients (112 male, mean age: 61.8 years); 133
- 1548 (66.8%) were macroreentrant and 66 (33.2%) were scar-related reentry circuits. The MB network participated in 60
- 1549 (30.2%) reentrant ATs: 31 perimitral ATs (PMATs) and 29 localized reentry circuits. Of 60 MB-related ATs, 49
- 1550 (81.6%) terminated with RF ablation: 44 (73.3%) at the MB-LA junction and 5 (8.3%) at the MB-CS junction,
- 1551 while 9 (15%) terminated after 2.5–5 cc of ethanol infusion inside the vein of Marshall (VOM). Of the 31 PMATs,
- 1552 17 (54.8%) terminated at the MB-LA junction, 5 (16.1%) at the MB-CS junction, and 7 (22.6%) with ethanol
- 1553 infusion. Of the 29 localized reentry circuits using the MB, 27 (93.1%) terminated at the MB-LA junction, none at
- 1554 the MB-CS junction, and 2 (6.9%) after ethanol infusion. Recurrences were mostly observed after RF ablation (18
- 1555 of 37 patients, 49%) compared to ethanol infusion (1 of 9 patients, 11%) (P=0.06).
- 1556



1557 Figure 5-5. Classification and termination sites of Marshall Bundle related ATs after AF ablation

1558

1559 Summary and conclusion

1560 The main findings of our study are as follows:

- 1561 (1) The MB is involved in a higher proportion of post-AF ablation ATs than previously reported.
- 1562 (2) Of MB-related ATs, 51.7% were MATs and 48.3% were localized reentry ATs.
- 1563 (3) MB-related ATs can be successfully terminated with RF ablation, either endocardially via MB-LA connection
- 1564 or epicardially via MB-CS connections (at the ostium of the VOM), and with ethanol infusion inside the VOM
- 1565 under the guidance of high-resolution mapping system.
- 1566 In conclusion, we have demonstrated that MB reentrant ATs accounted for up to 30.2% of the left ATs after AF
- ablation. Ablation of the MB-LA or CS-MB connections guided by the high-resolution mapping system or ethanol
- 1568 infusion inside the VOM can successfully terminate these ATs.
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The role of Marshall bundle epicardial connections in atrial tachycardias after atrial fibrillation ablation @

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BACKGROUND Atrial tachycardias (ATs) are often seen in the context of atrial fibrillation (AF) ablation.

OBJECTIVES To evaluate the role of the Marshall bundle (MB) network in left atrial (LA) ATs using high-density 3-dimensional mapping.

METHODS A total of 199 ATs were mapped in 140 patients (112 male, mean age: 61.8 years); 133 (66.8%) were macroreentrant and 66 (33.2%) were scar-related reentry circuits. MB-dependent ATs were suggested by activation mapping analysis and confirmed with entrainment along the circuit.

RESULTS The MB network participated in 60 (30.2%) reentrant ATs: 31 perimitral ATs (PMATs) and 29 localized reentry circuits. Of 60 MB-related ATs, 49 (81.6%) terminated with radiofrequency (RF) ablation: 44 (73.3%) at the MB-LA junction and 5 (8.3%) at the MB-coronary sinus (CS) junction, while 9 (15%) terminated after 2.5–5 cc of ethanol infusion inside the vein of Marshall (VOM). Of

Atrial tachycardias (ATs) are often seen in the context of atrial fibrillation (AF) ablation.¹ These ATs may be macroreentrant ATs (MATs) or scar-related reentrant ATs.² The ligament of Marshall is an epicardial vestigial fold that contains the vein of Marshall (VOM) and a myocardial sleeve called the Marshall bundle (MB); it has previously been implicated as a source of focal activity initiating AF.³ Radio-

Conflicts of interest: The authors declare no conflicts of interest. Funding: None. Address reprint requests and correspondence: Dr Nicolas Derval, Hôpital Cardiologique du Haut-Lévêque, CHU Bordeaux, LIRYC, L'institut de rythmologie et modélisation cardiaque, Université de Bordeaux, Avenue du Haut Lévêque, 33600 Pessac, Frankreich, Bordeaux, France. E-mail address: dervalnicolas@gmail.com. the 31 PMATs, 17 (54.8%) terminated at the MB-LA junction, 5 (16.1%) at the MB-CS junction, and 7 (22.6%) with ethanol infusion. Of the 29 localized reentry circuits using the MB, 27 (93.1%) terminated at the MB-LA junction, none at the MB-CS junction, and 2 (6.9%) after ethanol infusion. Recurrences were mostly observed after RF ablation (18 of 37 patients, 49%) compared to ethanol infusion (1 of 9 patients, 11%) (P = .06).

CONCLUSIONS MB reentrant ATs accounted for up to 30.2% of the left ATs after AF ablation. Ablation of the MB-LA or CS-MB connections or ethanol infusion inside the VOM is required to treat these arrhythmias.

KEYWORDS Atrial fibrillation; Atrial tachycardia; Catheter ablation; Epicardial connections; Marshall bundle

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frequency catheter ablation (RFCA) is an effective therapy for patients with AF, but perimitral ATs (PMATs) and localized reentry circuits commonly develop after pulmonary vein isolation (PVI) with or without additional left atrial ablation, or after mitral valve surgery.^{4,5} The MB has variable connections to the adjacent myocardium. Patients who have more than 2 connections between the MB and the myocardium of the coronary sinus (CS), left atrium (LA), or pulmonary veins have the anatomical substrate to generate localized reentry circuits or macroreentrant ATs around the mitral isthmus, using the epicardial MB.^{3,6} Macroreentry using the MB has recently been reported in case series,⁷ but localized reentry circuits using the MB post AF ablation have not been evaluated. Recent

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improvements in catheter and electroanatomic mapping technology have allowed significant improvements in the identification of the precise circuits of post–AF ablation ATs.^{4,8} This study was conducted to clarify the electrophysiological characteristics of MB-dependent ATs presenting after AF ablation.

Methods

Patient population

We analyzed tachycardia activation maps and entrainment data for 140 consecutive patients (112 [80%] male, mean age: 61.8 years) referred for ablation of left ATs guided by the Rhythmia system (Cambridge, MA). All had undergone AF ablation and were resistant or intolerant to at least 1 antiarrhythmic drug (AAD). We excluded from our study all right ATs, biatrial tachycardias, and ATs unable to perform activation mapping and identify the mechanism of the arrhythmia (cycle length variability, nonsustained AT, AT changing to another AT or AF during mapping). All patients gave written informed consent and the study protocol was approved by the local Research and Human Ethics Committees.

Previous ablation

All patients had undergone a previous ablation procedure for persistent AF. In the index ablation procedure PVI at the PV-LA junctions was always performed at the outset. Following PVI, we used 2 ablation protocols: (1) electrogram (EGM)-guided ablation using the stepwise approach⁹ (including PVI and then ablation of complex fractionated atrial EGMs, linear ablation at the LA roof, mitral isthmus and cavotricuspid isthmus, right atrial ablation); or (2) noninvasive mapping with an array of body surface electrodes and computed tomographybased cardiac geometry (ECVUE, CardioInsight Technologies Inc, Cleveland, OH).¹⁰ In both approaches the aim was AF termination to an organized rhythm (sinus rhythm or AT).

Ultrahigh-resolution electroanatomic mapping

Antiarrhythmic medications (except for amiodarone) were discontinued at least 5 half-lives prior to the procedure. Patients were anticoagulated for at least 1 month prior to the procedure and underwent transesophageal echocardiography or computed tomography scan within 48 hours preceding the procedure to exclude the presence of thrombus and delineate LA anatomy. All procedures were performed with an uninterrupted anticoagulation regimen. Mapping procedure details have been previously reported.^{4,11} Briefly, an IntellaMap Orion basket catheter was used to generate an atrial map. When patients were in sinus rhythm at the beginning of the procedure, AT was induced with burst pacing. Activation and voltage maps were studied without changing the automatic timing annotation of the system.

Bipolar propagation maps were reviewed in detail for sites of epicardial–endocardial breakthrough (EEB), defined as (1) the presence of a focal endocardial activation with radial spread (which could therefore not be accounted for by an endocardial wavefront) and (2) present with the same timing on every tachycardia cycle. Bipolar and unipolar EGMs at the site of focal breakthrough were individually analyzed to confirm the direction of activation. The size of the focal breakthrough was defined by the area of electrodes activated within 5 ms of the earliest breakthrough. The morphology of the unipolar EGMs at the site of focal breakthrough was also analyzed; a QS pattern was considered consistent with focal activation and an rS pattern suggested breakthrough from an epicardial site.

Diagnosis of AT using the MB

As previously reported,^{4,5} we classified left-sided ATs according to activation, as follows (Supplemental Figure 1): (1) MATs using anatomical obstacles or PV-encircling lesions to sustain the reentrant circuit; (2) scar-related localized reentry circuits not using anatomical obstacles.

We used the following criteria to link the Marshall network with the clinical AT (Supplementary Table 1):

1: Exclusion of conventional MAT

- Postpacing interval (PPI)-tachycardia cycle length (TCL) >20 ms at anterior and posterior LA walls to exclude roof-dependent MATs
- PPI-TCL >20 ms at septal or lateral aspects of the mitral annulus to exclude perimitral MATs
- 2: CS activation pattern
 - Distal-to-proximal CS activation or mid-CS activation preceding proximal and distal CS activation.
- 3: AT circuit colocalizing with the VOM
- 4: Missing part of the circuit endocardially in activation mapping (missing >10% of the TCL)
- 5: Entrainment mapping suggesting that the MB is in the active part of the circuit
 - PPI-TCL ≤20 ms at the left lateral ridge, posterior base of the left atrial appendage (LAA), inferolateral LA (overlying the CS), and/or the mid-to-distal CS region
- 6: Unipolar recordings showing rS patterns in the EEBs (MB-LA connections)

Two types of MB-related ATs were identified according to the anatomic distribution of the VOM (Supplemental Figure 1): MB-macroreentrant AT (Supplemental Figure 2) and localized reentry circuits using the MB around the left pulmonary veins (LPVs)-LAA base junction (Supplemental Figure 3). Supplemental Table 1 and Supplemental Figures 1, 2, and 3 delineate the criteria used to differentiate MB-related ATs.

Ablation of ATs using the MB

RFCA was performed in reentrant circuits to disrupt the circuit with a line applied between 2 anatomic barriers. Ablation was performed using a 3.5-mm open irrigated catheter (THERMOCOOL SF Catheter, Biosense Webster, Diamond Bar, CA) with energy of 35–45 W. Specifically, we applied radiofrequency (RF) energy at 35–45 W at the ridge-LPV junction and LAA base (MB-LA connection) or 20–25 W at the bifurcation of the CS and VOM (CS-MB connections).

If the AT terminated during RF ablation, incremental atrial pacing to a minimum pacing cycle length of 200 ms was performed in an attempt to reinduce the arrhythmia. If it remained noninducible, the ablation was considered successful. When linear ablation was used across an isthmus, activation mapping during LAA pacing or CS distal pacing or differential pacing on either side of the ablation line was performed to confirm bidirectional block.¹¹

We analyze the technique for VOM venography and ethanol injection into the VOM in the supplementary file.

Follow-up

All patients were anticoagulated for at least 3 months postprocedure or indefinitely, according to the CHA_2DS_2 -VASc score. Twelve-lead electrocardiogram, 24-hour Holter, and echocardiography were regularly performed 1, 3, 6, 9, and 12 months after discharge and every 6 months thereafter, with additional visits if patients described palpitations. All patients were followed up for at least 18 months after the first procedure. AADs were permitted only for the first 3-month blanking period. We defined arrhythmia recurrence as any episode of documented AF/AT >30 seconds or use of AADs after the initial 3-month blanking period, or a second LA ablation procedure for AF/AT at any time.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD), while categorical ones are presented as absolute and relative frequencies (percentages). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with and without normal distribution were compared using Student *t* test or the Mann-Whitney *U* test, respectively. Pearson χ^2 or Fisher exact test were used to test for any associations between 2 categorical variables. Analyses were done with SPSS (version 17.0, SPSS Inc, Chicago, IL) and all reported *P* values are 2tailed, with a significance level of .05.

Results

Clinical characteristics

Data regarding the clinical characteristics of the patients are summarized in Supplemental Table 2. The mean age of the cohort was 61.8 years. All patients (140 patients) had undergone at least 1 previous ablation procedure (mean: 2.9 ± 1.5) including PVI, either as a standalone procedure or combined with mapping and ablation of AT. Ninety-one (65%) patients presented with left ATs after ablation for persistent AF using the stepwise approach and 49 (35%) patients using the body-surface mapping system (ECVUE). There were no significant differences in the clinical characteristics, including the age, sex, left ventricular ejection fraction, hypertension, stroke, heart failure, and CHA₂DS₂-VaSc score, between MB-related ATs and ATs not related to the MB. We excluded from our study 26 patients: 13 with right ATs, 6 with biatrial tachycardias, and 7 with ATs unable to map and identify the mechanism of the arrhythmia from activation mapping.

Electrophysiological characteristics of 199 left ATs after AF ablation

Supplemental Table 3 summarizes the electrophysiological characteristics of the 199 left ATs included in our study. The mean AT cycle length was 278.8 ± 73.2 ms. Maps were created in 14.8 ± 12.9 minutes, with $18,846 \pm 10,888$ mapping points collected from 2015 ± 1554 beats, and an LA volume of 166.9 ± 53.7 mL. A total of 133 ATs (66.8%) were MATs using anatomical obstacles and 66 (33.2%) were scar-related reentrant ATs (non-MATs). The MB was found to participate in 60 (30.2%) ATs, 31 (23.3%) MATs (29 perimitral and 2 double-loop reentry using mitral isthmus and roof), and 29 (43.9%) scar-related localized reentry circuits (Figure 1).

Electrophysiological characteristics of MB-related ATs

Sites of endocardial-epicardial breakthrough

Analysis of the unipolar EGMs in the EEB sites at the MB-LA junction demonstrated a mean area of MB-LA connections of 0.71 ± 0.23 cm². The mean number of EGMs evaluated at each EEB site was 101 ± 41 . Unipolar EGMs at the site of EEB had an rS pattern in all MB-related ATs.

EGM characteristics of the MB

High-frequency multiphasic fragmented EGMs with long duration were recorded endocardially or epicardially in the MB region (MB-LA or MB-CS connections). The amplitude of these signals was 0.5 ± 0.79 mV vs 0.26 ± 0.28 mV (P = 1.00) and the duration was 65 ± 40 ms vs 122 ± 67 ms (P = .005) for MB-PMATs and MB-localized reentry circuits, respectively. The duration of the high-frequency multiphasic fragmented EGMs in MB-LA or MB-CS connections was significantly longer in MB-localized reentry circuits than in MB-macroreentrant ATs (122 ± 67 ms vs 65 ± 40 ms, P = .005) (Table 1). MB-LA connections were identified at the ridge between LPVs and posterior base of the LAA, correlating with the arborization of the VOM. MB-CS connections were identified in the region surrounding the ostium of VOM.

Termination sites of MB-related ATs

Of 60 MB-related ATs, 49 (81.6%) were terminated with RF ablation (44 [73.3%] at the MB-LA junction [at the ridge between the LPV and the base of the LAA] and 5 [8.3%] at the MB-CS junction), while 9 (15%) terminated after 5 cc of ethanol infusion inside the MB (Figure 1). Of the 31 MB-dependent MATs (Figure 2), 17 (54.8%) terminated at the MB-LA junction, 5 (16.1%) at the MB-CS junction, and 7 (22.6%) were terminated with ethanol infusion inside the



Figure 1 Classification and termination sites of Marshall bundle-related atrial tachycardias after atrial fibrillation ablation. AT = atrial tachycardia; CS = coronary sinus; LA = left atrium; MB = Marshall bundle.

VOM. We were unable to terminate 2 MATs (6.5%) with RF energy, either endocardially at the MB-LA junction or epicardially at the MB-CS junction. We were further unable to identify or cannulate the VOM and thus were unable to perform ethanol infusion. The mean time for termination was 286.6 \pm 177.4 seconds in patients with RF ablation and 107.6 \pm 217.3 seconds in patients with ethanol infusion. Of the 29 MB-dependent localized reentry circuits (Figure 3), 27 (93.1%) were terminated at the MB-LA junction, none at the MB-CS junction, and 2 (6.9%) after ethanol infusion. The mean time for termination was 61.9 ± 96.8 seconds with RF ablation and 32.5 ± 10.6 seconds after ethanol infusion. Figure 4 summarizes the termination sites of MB-related ATs, either with RF ablation in the MB-LA connections or MB-CS connections, or with ethanol injection into the VOM. Supplemental Figure 4 demonstrates an example of an MB-related AT converted from an anterior localized reentry circuit with passive MB activation.

Postablation management and follow-up

After a mean follow-up of 18 months, 19 of 46 patients (41.3%) with MB-related ATs had atrial arrhythmia recur-

rence after 18 months of follow-up. Of the 37 patients in whom MB-related ATs were terminated with RF energy either endocardially at the MB-LA junction or epicardially at the MB-CS junction, 18 patients (48.6%) had atrial arrhythmia recurrence. Of the 9 patients that underwent ethanol injection, only 1 (11.1%) had atrial arrhythmia recurrence during 18 months of follow-up (P = .06).

Discussion

The main findings of our study are as follows: (1) the MB is involved in a higher proportion of post-AF ablation ATs than previously reported (30.2%); (2) of MB-dependent ATs, 51.7% were MATs and 48.3% were localized reentry circuits; (3) the MB network, endocardially via MB-LA connections and epicardially via MB-CS connections, has specific EGM patterns; (4) MB-related tachycardias can be terminated with RF ablation, either endocardially via MB-LA connection or epicardially via MB-CS connections (at the ostium of the VOM), and with ethanol infusion inside the VOM; and (5) although results were not statistically significant, patients with MB-related ATs that underwent ethanol

Table 1 Electrophysiological characteristics of Marshall bundle-related atrial tachycardias

| EP characteristics of the 60 MB-related ATs | MB-localized reentrant ATs | MB-macroreentrant ATs | P values |
|---|----------------------------|-----------------------|----------|
| AT cycle length (ms) | 284.86 ± 70.79 | 264.45 ± 75.46 | .39 |
| LA volume (mL) | 162.17 ± 51.46 | 163.93 ± 56.55 | .9 |
| LA mapping time (s) | 871.46 ± 542.58 | 725.14 ± 603.33 | .34 |
| LA mapping points | 19112 ± 12057 | 20903 ± 12359 | .48 |
| LA mapping beats | 1890 ± 1366 | 2201 ± 1462 | .43 |
| Amplitude of fragmented signal in MB-LA connection (mV) | 0.26 ± 0.28 | 0.50 ± 0.79 | 1.00 |
| Longest duration of the fragmentation in the MB-LA | 122.8 ± 67.2 | 62.2 ± 40.1 | .005 |

Continuous data are presented as mean \pm standard deviation (SD).

AT = atrial tachycardia; EP = electrophysiological; LA = left atrium; MB = Marshall bundle.



Figure 2 Counterclockwise perimitral atrial tachycardia (AT) using epicardial connections of the Marshall bundle (MB). (1) Left atrial activation maps covered $\leq 90\%$ of tachycardia cycle length (TCL), missing 28% of the TCL (81 ms). (2) Postpacing interval (PPI)-TCL ≤ 20 ms at the vein of Marshall (VOM), the ridge of left pulmonary veins-posterior base of the left atrial appendage (LPVs-LAA), the anterior wall of the left atrium (LA), and 6 to 11 o'clock of the mitral annulus. (3) PPI-TCL ≥ 20 ms at the distal coronary sinus, the posterior wall of the LA, and the mitral isthmus. MB-macroreentrant AT was terminated to sinus rhythm after 5 cc ethanol injection into the VOM.

infusion had a better outcome regarding atrial arrhythmia recurrence at 18 months' follow-up in comparison with patients in whom we performed only RF energy (11.1% vs 48.6%, P = .06).

In our study, MB-related ATs occur more frequently (30.2%) after AF ablation than previously described in case series.⁷ Hayashi and colleagues⁷ reported that following PVI or valve surgery, they accounted for up to 11% of



Figure 3 Localized reentrant atrial tachycardia (AT) using the Marshall bundle (MB) around the left lateral ridge-left pulmonary veins (LPVs), and base of the left atrial appendage (LAA). (1) Activation mapping \geq 75% tachycardia cycle length (TCL) but <90% TCL (299 ms), missing 26% of the TCL (79 ms). (2) Postpacing interval (PPI)-TCL \leq 20 ms at the left lateral ridge, posterior base of the LAA. (3) PPI-TCL >20 ms in the septal mitral annulus and proximal and distal coronary sinus. Recordings in the ligament of Marshall-left atrial (LA) connections displayed high-frequency long-duration amplitude multicomponent (multiphasic) electrograms. The amplitude and duration of electrograms in the MB-LA connection (ridge-LPV, base LAA) was 0.2 mV and 83 ms, respectively. MB-related AT was terminated to sinus rhythm after 5 cc alcohol injection into the vein of Marshall.

PMATs. In addition, in our study we showed that the MB is related not only to MATs, but also to localized reentry circuits turning around the ridge-LPV junction and LAA base. The proarrhythmogenic potential of the MB has previously been reported in animal and human studies. Scherlag and colleagues¹² have reported in a canine model that the muscle fibers of the VOM were part of an interatrial connection. They recorded discrete double potentials, representing distinct activation of the local atrial myocardium and MB fibers.¹² In humans, the MB has been shown to be a more complex structure than in the canine heart, with multiple insertions to the LA myocardium and CS.13 These connections provide substrate for reentry, and several recent case series have described reentrant tachycardias dependent on activation within the MB.^{7,13} Owing to the protected nature of the VOM myocardium and the complex nature of AT circuits contained within a small region of myocardium, determination of the involvement of the MB in a post-AF ablation AT can be difficult, particularly with large, widely spaced recording electrodes.¹⁴ Here we present a detailed study, using high-density mapping with small, closely spaced electrodes and entrainment maneuvers, to quantify and characterize the involvement of the MB in ATs presenting after LA ablation for AF.

The MB is an electrically protected, isolated anatomical structure, difficult to target with RFCA.¹² Endocardial ablation from within the LA may not successfully ablate the MB, owing to the distance from endocardium to MB and the presence of overlying epicardial fat. In RF ablation, the heating of cardiac tissue is mainly resistive and MB is affected probably only owing to heat diffusion.¹⁵ These difficulties may, at least in part, explain the high failure rate of mitral isthmus block in published studies.^{16,17} This is the main rationale to select "MB-LA connections" and/or "MB-CS connections" as a primary ablation target in MBrelated ATs or to choose ethanol infusion rather than endocardial ablation of the LA facing the anatomical distribution of the VOM. Previous studies have described successful ablation of the MB at several points along its course, at the mitral annulus, at the lateral ridge/PV antrum,6.7 and epicardially in the CS and the VOM itself.^{6,18} Ethanol infusion inside the VOM has also been described in case series and may be an adjunctive or standalone strategy in patients with refractory MB-related perimitral ATs or MBdependent localized reentry circuits.6,18,19 The additional use of ethanol MB ablation seems to improve ablation rates, when compared with RF ablation alone.^{6,16,17} These findings are in agreement with our study, as we demonstrated that ethanol injection is more effective than using RF energy for ablation regarding transmurality and durability of the lesions. Only 1 out of 9 patients in whom we used ethanol injection to terminate MB-related ATs had atrial arrhythmia recurrence at 18 months of follow-up. Of the 37 patients in whom MB-related ATs were terminated with RF energy either endocardially at the MB-LA junction or epicardially at the MB-CS junction, 18 (48.6%) had atrial arrhythmia recurrence (P = .06).



Figure 4 Of the 31 Marshall bundle (MB)-dependent macroreentrant atrial tachycardias (MATs), 17 (54.8%) terminated at the MB-left atrial (LA) junction, 5 (16.1%) terminated at the MB-coronary sinus (CS) junction, and 7 (22.6%) were terminated with alcohol infusion inside the vein of Marshall (VOM). We were unable to terminate 2 MATs (6.5%) with radiofrequency energy, either endocardially at the MB-LA junction or epicardially at the MB-CS junction. We were further unable to identify or cannulate the VOM and thus unable to perform ethanol infusion. Of the 29 MB-dependent localized reentry circuits, 27 (93.1%) were terminated at the MB-LA junction, no ewere terminated at the MB-CS junction, and 2 (6.9%) were terminated after ethanol injection.

MB-specific electrophysiological pattern

The bipolar EGMs recorded in MB-LA connections and MB-CS connections have a characteristic electrophysiological pattern: high-frequency long-duration amplitude multicomponent (multiphasic) EGMs (Figure 4). Other groups have also reported fractionated potentials at the MB-LA junction, lasting >100 ms, in small numbers of patients with MBrelated perimitral ATs,⁷ and conduction abnormalities have been reported along the epicardial fiber network at the junction between the MB and Bachmann bundle, potentially related to the development of AF reentry mechanisms in selected patients.²⁰ Unipolar EGMs at the site of the MB-LA junction had an rS pattern in all MB-related ATs. This is consistent with epicardial-to-endocardial breakthrough from the MB at this site, rather than focal activation. Epicardial-to-endocardial connections may play a wider role in other atrial tachyarrhythmias. An epicardial mapping study of 24 patients with long-standing persistent AF has described the presence of focal fibrillation waves in which a small R wave could be recorded on unipolar recording, favoring EEB rather than a focal mechanism.²

Clinical implications and future perspectives

Bidirectional mitral isthmus block is a key endpoint for ablation in many patients with atrial tachyarrhythmias. The high failure rate of mitral isthmus ablation may contribute to the poor success of adding linear ablation to PVI for persistent AF in some clinical trials.²² Techniques for ablating the MB are likely to improve mitral isthmus bidirectional block rates (Supplemental Figure 5). Furthermore, the VOM has been implicated in the pathogenesis of AF, both as a source of focal ectopic beats that trigger AF¹⁸ and a source of parasympathetic²³ and sympathetic¹³ innervations that modulate electrical properties of atrial tissue and contribute to AF maintenance.²⁴ These properties also make the VOM an attractive target during ablation of AF.

Limitations

Firstly, it is not possible to generalize the findings of this study to naïve AT patients or patients only having undergone PVI, as atypical atrial flutter with complex reentry circuits may occur owing to extensive ablation during the previous, possible multiple, procedures, or even through progressive remodeling. Secondly, the role of the MB in post-AF AT ablation may be underestimated in our study, because ATs that we considered conventionally mitral isthmus dependent may have had simultaneous epicardial activation using the MB as well as endocardial activation in the ridge-LPV junction/LAA base and posterior mitral isthmus region. Thirdly, it is important to consider that, as we did not systematically perform recording of the activation of the VOM using the
2F catheter electrode catheter (EPstar, Japan Lifeline Corp, Tokyo, Japan), some of these ATs may arise not from the MB itself but from other epicardial anatomical structures. For example, the left lateral ridge comprises the leftward extension of the Bachmann bundle, with the inferior branches of the septopulmonary bundle and the septoatrial bundle giving rise to significant crossover arrangements of the myocardial fibers transmurally. In 30% of hearts there are extra-appendicular muscular trabeculations connecting the ridge to the vestibule of the mitral annulus, and in the majority of hearts the VOM is 3 mm from the endocardium of the ridge and has muscular connections to the PVs.

Conclusion

MB reentrant ATs accounted for up to 30.2% of the left ATs after AF ablation. Ablation of the MB-LA or CS-MB connections or ethanol infusion inside the VOM is required to treat these arrhythmias.

Appendix Supplementary data

Supplementary data associated with this article can be found

in the online version at https://doi.org/10.1016/j.hrthm.2019. 05.019.

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5-6. Mechanism of recurrence of AF ablation related atrial tachycardia: Comparison between index vs. redo procedures in high-resolution mapping system.

1588

1589 Background and purpose of the study

- 1590 Despite superior accuracy and understanding of mechanisms using high-resolution mapping as described above, we
- 1591 still experience recurrence of ATs. In this study, we tried to understand the mechanism of these recurrences. It is of
- 1592 major importance to understand whether these ATs are true failures due to reconduction across previous ablation, or
- 1593 new ones due to progression of atrial remodeling. The purpose of this study was to compare the mechanism of the
- 1594 ATs between the index and the redo procedure in AF ablation related AT (AFA-rAT) patients.



Figure 5-6-1. Flow-chart showing the study population

1595

1596 Methods and results

1597 The mechanism of ATs diagnosed by the 'RhytmiaTM' high-resolution mapping system was compared between the 1598 first ablation and the redo procedure in 37 patients described in **Figure 5-6-1**.

- 1599 We classified ATs according to the activation pattern: focal AT, AMAT, and Non-AMAT (localized reentry). AMATs
- 1600 included PTF, PMF, and RMAT. Others were all defined as Non-AMAT.
- 1601 The comparison between the index AFA-rATs and redo AFA-rATs is described in **Table 5-6**. Occurrence of PMF in
- 1602 the index procedure predicted the same AT circuit in the redo procedure with 78.9% sensitivity, 38.9% specificity,
- 1603 57.7% positive predictive value (PPV) and 63.6% negative predictive value (NPV).
- 1604 RMAT in the index procedure predicted the same AT in the redo procedure with 80.0% sensitivity, 63.0% specificity,
- 44.4% PPV and 89.5% NPV. PTF in the index procedure predicted the same AT with 0% sensitivity, 72.2% specificity,
 0% PPV and 96.3% NPV.
- 1607 Non-AMAT in the index procedure predicted the Non-AMAT (but not the same Non-AMAT) with 41.7% sensitivity,
- 1608 64.0% specificity, 35.7% PPV and 69.6% NPV, although the most circuits were different between the index and the
- 1609 redo procedure. Absence of focal ATs at the index procedure predicted the absence of focal ATs at the second
- 1610 procedure with a NPV of 97.1%.
- 1611

1612 Table 5-6. Relation between the index and the redo procedure

Relation between the index and the redo procedure in patients with PMF

| · · · · · · · · · · · · · · · · · · · | | |
|---|---|---|
| | PMF (+) in the redo procesure (N=19) | PMF (-) in the redo procesure (N=18) |
| PMF (+) in the index procedure (N=26) | 15 | 11 |
| PMF (-) in the index procedure (N=11) | 4 | 7 |
| Relation between the index and the redo procedu | re in patients with RMAT | |
| | RMAT (+) in the redo procedure (N=10) | RMAT (-) in the index procedure (N=27) |
| RMAT (+) in the index procedure (N=18) | 8 | 10 |
| RMAT (-) in the index procedure (N=19) | 2 | 17 |
| Relation between the index and the redo procedu | re in patients with PTF | |
| | PTF $(+)$ in the redo procedure (N=1) | PTF (-) in the redo procedure (N=36) |
| PTF (+) in the index procedure (N=10) | 0 | 10 |
| PTF (-) in the index procedure (N=27) | 1 | 26 |
| Relation between the index and the redo procedu | re in patients with Non-AMAT | |
| | Non-AMAT (+) in the redo procedure (N=12) | Non-AMAT (-) in the redo procedure (N=25) |
| Non-AMAT in the index procedure (+) (N=14) | 5 | 9 |
| Non-AMAT (-) in the index procedure (N=23) | 7 | 16 |
| Relation between the index and the redo procedu | re in patients with focal AT | |
| | Focal AT (+) in the redo procedure (N=1) | Focal AT (-) in the redo procedure (N=36) |
| Focal AT (+) in the index procedure (N=3) | 0 | 3 |
| Focal AT $(-)$ in the index procedure (N=34) | 1 | 33 |

1613 Incidence of ATs using epicardial structures was described in the Figure 5-6-2. ATs using epicardial structures were

1614 observed in 18/37 (48.6%) patients. Epicardial structure related ATs were identified in 15/19 (79.0%) PMF, 3/10

1615 (30.0%) RMAT, and 4/12 (33.3%) Non-AMATs. In most cases, the structure used for the epicardial circuit was the

1616 CS/VOM system (n=16).



Epicardial structures are highly involved in recurrent cases of AF ablation related ATs





1619

1620 Summary and conclusion

We have demonstrated that: (1) PMF is the most common type of recurrence of the AFA-rAT. Redo AFA-rAT ablation procedures demonstrated a true failure rate of 57.7%, followed by RMAT, with a true failure at 44.4%. (2) Epicardial structures were included in the circuit in 78.9% of PMF, 30.0% of RMATs, and 33.3% of Non-AMATs. The very high true failure rate in PMF may be explained by the highest involvement of epicardial structures. (3) Non-AMATs (localized ATs) are frequent, both in the index and redo AT procedures, but the circuit is usually different. (4) Information of ATs in the index procedure is useful to guide the redo procedure of AFA-rAT.

1627

In conclusion, PMF should be frequently considered in the mechanism of recurrence after ablation of AFA-rAT, regardless of the prior procedures. When RMAT, CTI-dependent AT or focal AT was not identified in the index AT procedure, these ATs were highly unlikely to be present in the redo AT procedure. Although Non-AMAT may be possible in the redo procedure when it is identified in the index session, the circuit may be different. Approximately 60% of patients developed recurrent ATs related to epicardial structures, and the incidence is especially high in PMF. CS and VOM, is important structure which can bypass endocardial activation.

- 1634
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1637

1638 Mechanism of recurrence of AT: Comparison between first vs. redo procedures in high-resolution mapping

1639 system.

- 1640 **Takigawa M**, Derval N, Martin C, Vlachos K, Denis, A, Kitamura T, Cheniti G, Bourier F, Lam A, Martin R,
- 1641 Frontera A, Thompson T, Massoullié G, Wolf M, Escande W, André C, Zeng LJ, Nakatani Y, Roux JR; Duchateau
- 1642 J, Pambrun T, Sacher F, Cochet H, Hocini M, Haïssaguerre M, Jaïs P.

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| 2 | high-resolution mapping system. |
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| 3 | |
| 4 | |
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Mechanism of recurrence of AT: Comparison between first vs. redo procedures in

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12

1

13 Running Title: Mechanism of recurrence of AFA-rAT

14

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| 26 | 6677 words; 3 tables; 4 figures; 28 references |
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| 27 | |
| 28 | |
| 29 | ABSTRACT |
| 30 | |
| 31 | Background: Atrial fibrillation (AF) ablation related atrial tachycardia (AFA-rAT) is complex, and |
| 32 | may demonstrate several forms: anatomical macroreenrant AT (AMAT), Non-AMAT, and focal AT. |
| 33 | |
| 34 | Objectives: The purpose of this study was to elucidate the recurrence rate and mechanisms of |
| 35 | AFA-rAT recurrence. |
| 36 | |
| 37 | Methods: Among 147 patients with ATs, 68 (46.3%) had recurrence at mean 5.9 [3.1-11.3] months |
| 38 | and were mapped and ablated using the Rhythmia system. The circuits of the first AT were |
| 39 | compared to those in the redo procedure in 37 patients who had had at least one mappable AT at the |
| 40 | first procedure and who received a redo procedure. |
| 41 | |
| 42 | Results: These 37 patients (62+/-9yrs, 8 females) had shown 68 ATs during the first procedure; 26 |
| 43 | peri-mitral flutter (PMF), 18 roof-dependent macroreentrant-AT (RMAT), 10 peri-tricuspid flutter |
| 44 | (PTF), 14 Non-AMAT, 3 focal AT. During the redo AT ablation procedure, 43 ATs were observed; |
| 45 | 19 PMF, 10 RMAT, 1 PTF, 12 Non-AMAT, 1 focal AT. Recurrence of PMF and RMAT was |
| 46 | observed in 15/26 (57.7%) and 8/18(44.4%) respectively, while PTF did not recur. Neither the same |
| 47 | focal AT nor the same Non-AMAT were observed except in one case with septal scar related |
| 48 | biatrial-AT. Epicardial structure-related ATs were involved in 12/16 (75.0%) in PMF, 3/10 (30.0%) |
| 49 | in RMAT, and 4/12(33.3%) in Non-AMAT. Out of 18 patients with the circuit including epicardial |
| | |

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25

 $\mathbf{2}$

- 50 structures, 6 patients treated with ethanol-infusion in the vein of Marshall (VOM) did not show any
- 51 AT-recurrence, though 6/12 (50.0%) treated with RF showed AT-recurrence (P=0.05).
- 52
- 53 Conclusions: Although high-resolution mapping may lead to correct diagnosis and appropriate
- 54 ablation in the first procedure, the recurrence rate is high. The main recurrent mechanism of
- 55 AFA-rAT is the recurrence of PMF and RMAT, or Non-AMAT different from the first procedure.
- 56 Epicardial structures (e.g. coronary sinus/VOM system) is often involved, and ethanol-infusion in the
- 57 VOM may be an optional treatment.
- 58
- 59 Keywords: Atrial tachycardia; high-resolution mapping; epicardial conduction; catheter ablation;
- 60 reentrant tachycardia
- 61
- 62
- 63
- 64

- 65 AF, atrial fibrillation
- 66 AFA-rAT, atrial fibrillation ablation related atrial tachycardia
- 67 AMAT, anatomical macroreentrant atrial tachycardia
- 68 AT, atrial tachycardia
- 69 CL, cycle length
- 70 CS, coronary sinus
- 71 EI-VOM, ethanol infusion in the VOM
- 72 LA, left atrium
- 73 LAA, left atrial appendage
- 74 LAV, left atrial volume
- 75 LAVI, left atrial volume index
- 76 **PMF**, perimitral flutter
- 77 **PPI**, post pacing interval
- 78 PTF, peritricuspid flutter
- 79 PV, pulmonary vein
- 80 RA, right atrium
- 81 **RPV**, right pulmonary vein
- 82 RMAT, roof-dependent macroreentrant tachycardia

- 83 TCL, total cycle length
- 84 VOM, vein of Marshall

Disclainerial and not co be further disclosed.

88 INTRODUCTION

| | | | - |
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| 90 | With the development of extensive substrate catheter and surgical ablation strategies for persistent |
|-----|--|
| 91 | atrial fibrillation (AF), there has been a concurrent rise in the incidence of iatrogenic atrial |
| 92 | tachycardias (AT), in particular demonstrating complex mechanisms and anatomical circuits ¹⁻⁵ . |
| 93 | High-resolution mapping displays the precise activation sequence of ATs to be visualised ²⁻⁶ , |
| 94 | allowing the operator to modify their strategy and select the most effective ablation line, which may |
| 95 | result in higher termination rates, fewer RF deliveries, and shorter ablation procedures. 7-8 |
| 96 | However, despite superior accuracy and understanding of mechanisms using high-resolution |
| 97 | mapping, we still experience recurrence of ATs. It is of major importance to understand whether |
| 98 | these ATs are true failures due to reconduction across previous ablation, or new ones due to |
| 99 | progression of atrial remodeling. The purpose of this study was to compare the mechanism of the |
| 100 | ATs between the first and the redo procedure in AF ablation related AT (AFA-rAT) patients. |
| 101 | |
| 102 | METHODS |
| 103 | |

104

105 Study population

106 Between January 2015 and December 2016, 147 consecutive patients with clinically documented AT

107 following AF ablation (Supplemental Table 1 and 2) were treated using the 'Rhythmia'

108 high-resolution mapping system (Boston Scientific, Marlborough, US). Among them, no mappable

109 ATs were observed during the procedure in 29 patients, but at least one AT was mappable in the

remaining 118 patients. Among them 50 patients had a recurrence at a median of 5.9 [3.1-11.3]

111 months. To elucidate the mechanism of the recurrent AT, 37 patients who had had at least one

112 mappable AT and who agreed to receive a redo procedure were included in the analysis

113 (Supplemental figure 1). The mechanism of the recurrent AT with whom mappable ATs were not

114 observed during the first procedure was summarized in the supplemental figure 2.

115 The research was approved by local ethics committees. Prior written informed consent to participate

116 was obtained from all participants, according to institutional guidelines.

117

118 Electrophysiological study and mapping with Rhythmia

119 Electrophysiological study and mapping with the Rhythmia system was performed as previously

120 described^{2-4,8}. Antiarrhythmic medications were discontinued >5 half-lives prior to ablation with the

121 exception of amiodarone. A steerable decapolar catheter was introduced within the coronary sinus

122 (CS). If patients were in sinus rhythm at the beginning of the procedure, AT was induced with burst

123 pacing regardless of re-conduction or block of previous pulmonary vein (PV) or linear lesions. ATs

124 were mapped with the OrionTM multipolar basket catheter with support from a steerable long sheath

125 (Agilis:St Jude Medical or Zurpaz:Boston Scientific). An activation map was created under standard

126 automatic beat acceptance criteria based on (i) cycle length (CL) variation, (ii) activation time

127 difference variations between the CS electrograms, (iii) catheter motion, (iv) electrogram stability,

128 (v) catheter tracking quality, and (vi) respiration gating. Although the dense scar threshold was

129 nominally set at 0.03mV as a confidence mask parameter, it was manually lowered to be as close as

130 possible to the noise threshold, to allow visualization of the entire circuit.^{2-4, 8}

131

132 Definition

133 In the present study, the first procedure was defined as the procedure for AFA-rATs using the

¹³⁴ 'RhythmiaTM, mapping system for the first time regardless of the number of prior procedures for

135 AF/AT. A redo procedure was defined as the next procedure in patients with AT recurrence after the

136 first procedure. As mentioned above, the ultra-high density mapping system, RhythmiaTM, was also

137 used in these procedures.

138 We classified ATs according to the activation pattern: focal AT, anatomical macro-reentrant AT (AMAT), and Non-AMAT (localized reentry). As previously reported^{2,3,8}, AMATs included 139 140 peri-tricuspid flutter (PTF) dependent on the cavo-tricuspid isthmus, peri-mitral flutter (PMF) 141 dependent on the mitral isthmus, and RMAT (RMAT) dependent on the left atrial roof. Others were 142 all defined as Non-AMAT. Multiple-loop ATs were defined as those composed of more than 1 143 independent active circuit sharing one common isthmus, including dual-loop ATs and triple-loop ATs, with the entire CL included in each of the circuits.³ After the activation map was completed, 144 145 entrainment pacing was performed to confirm the diagnosis and circuit unless there were unstable 146 ATs or ATs with short CL (<200ms), where entrainment pacing might result in the conversion or 147 termination of the AT. 148 The commonest AT with epicardial conduction was CS/ Vein of Marshall (VOM) system-related AT 149 including PMF with CS/VOM and localized reentry around the left atrial appendage (LAA)-LPVs using the CS/VOM system as described in a previous paper⁹. When a PMF was using only the CS as 150 151 an epicardial conduction route, the activation map demonstrated a continuous jump over a line of 152 complete block on the mitral isthmus between the distal CS and the left lateral LA, and 153 PPI-TCL<20ms was confirmed at the circuit. When the PMF was using the VOM (+/- CS), the 154 activation map showed a jump between the inferolateral LA (overlying the CS) and/or the 155 mid-to-distal CS region, and the left lateral ridge, posterior base of the LAA with >10% TCL 156 missing, but the achievement of PPI-TCL <20ms was still confirmed in other parts around the mitral 157 annulus. RMAT around the left PVs can also use the CS/VOM system as an epicardial circuit. 158 Non-AMAT (Localized reentry) around the LAA-LPVs using the CS/VOM system also 159 demonstrated >10% TCL missing on the CS/VOM distribution. PPI-TCL 20ms was confirmed in 160 other parts of the localized circuit. Although endocardial high-output entrainment pacing with 161 PPI-TCL<20ms in the VOM distribution may be diagnostically important, it is not always possible 162 to capture the epicardial structure. Other epicardial conduction were relatively more difficult to

163prove, because the epicardial activation was not directly mapped. Although the epi- to endo-cardial164exit should show centrifugal activation similar to focal AT, PPT-TCL \leq 20ms at a large part of the165circuit may rule out a focal AT and raise the likelihood of an AT using epicardial structures such as166Bachmann's bundle.¹⁰

167

168 Catheter ablation

169 The appropriate ablation site was determined based on anatomical length, catheter stability, tissue 170 thickness and nearby vulnerable structures. In most cases, this represented the narrowest bridge of 171conducting tissue between scars or anatomical obstacles. The end-point for ablation, irrespective of the type of isthmus selected, was achievement of bidirectional conduction block ¹¹⁻¹⁴. PVs were 172 173 re-isolated in cases of reconduction. On completion of the procedure, entrance and exit PV block was 174 confirmed in all 4 veins and bidirectional conduction block was confirmed by differential pacing. In 175 particular, for the roof line and mitral isthmus line, differential pacing was performed with one 176 catheter left in the left appendage. Waiting time after the achievement of lesions or drug challenge 177 (adenosine and/or isoproterenol) were not systematically performed. In addition, non-inducibility of 178 the tachycardia after ablation was confirmed by incremental burst pacing up to a pacing cycle length 179 of 200ms or the local effective refractory period of the atrial tissue. Radiofrequency energy was 180 delivered using an irrigated 3.5-mm-tip ablation catheter (Thermocool® SF catheter, Biosense 181Webster, Diamond Bar, CA), with a power of 30-40 W and a cut-off temperature of 45°C. Generally, 182 the ablation catheter and strategy were the same between the first and the redo procedure. However, 183 ethanol-infusion of VOM (EI-VOM) was considered in some cases where the CS/VOM system 184 related AT was suspected to be included in the AT circuit. 185

186 Comparison of ATs between the first and the redo procedures.

187 The mechanism and circuit of ATs observed in the redo procedure was compared to those identified

188 in the first procedure.

189

190 Statistical analysis

- Data are expressed as mean ± standard deviation or/and median [25th-75th percentile] for continuous
 variables, and percentages for frequencies. To compare groups, chi-square analysis or Fisher's exact
- 193 test was used for categorical variables, and an ANOVA analysis or Kruskal-Wallis test was used for
- 194 continuous variables. P-values<0.05 were considered statistically significant.

195

196 RESULTS

- 197
- 198 Patient characteristics and the RhythmiaTM mapping data
- 199 Patient characteristics of the 37 patients (62+/-9 yrs, 8 females) that underwent a redo AT procedure
- 200 for recurrence of a AFA-rAT are shown in Table 1. Originally, all patients had persistent AF, with
- 201 18 having long-standing AF. Twenty of them had received ≥ 2 prior procedures, and 18 of them had
- 202 received ablation for ATs with a different mapping system. Mapping data of the 37 patients with the
- 203 Rhythmia system is summarized in the Table 2. Nine patients presented with SR and 28 with AT, at
- the start of the first procedure. Mean LA volume (LAV) was 152+/-32ml and 29 (78.4%) showed
- 205 severe LA enlargement with LAV index (LAVI) $>40m1/m^2$.

- 207 These patients demonstrated 68 ATs during the first procedure with the RhythmiaTM mapping system
- 208 as shown in Table 3 and 4: 3 (8.1%) focal AT, 26 (70.3%) PMF, 18 (48.6%) RMAT, 10 (27.0%)
- 209 PTF and 14 (37.8%) Non-AMAT. ATs were present spontaneously in 34 patients at the first

²⁰⁶

| 210 | procedure and successfully induced by pacing in the remaining 3 patients. In contrast, 43 ATs were |
|-----|---|
| 211 | identified during the redo AT procedure (Table 3 and 4): 1 (2.7%) focal AT, 19 (51.4%) PMF, 10 |
| 212 | (27.0%) RMAT, 1 (2.7%) PTF, and 12 (32.4%) Non-AMAT. Although ATs were present |
| 213 | spontaneously in 33 patients at the redo AT procedure, no ATs were inducible during the procedure |
| 214 | in 2 patients. Although the incidence of AMAT was significantly lower in the redo AT procedure |
| 215 | than in the first (P=0.02) as shown in Table 4, that of focal AT and non-AMAT was similar. |
| 216 | |
| 217 | Anatomical macro reentrant ATs |
| 218 | The prevalence of PMF in both first and redo procedures is summarized in Supplemental table 3. |
| 219 | PMF was observed in 26 patients at the first procedure (Figures 1A, 2A). Although the remaining 11 |
| 220 | patients did not have a clinical PMF, a mitral isthmus line was completed with bidirectional block |
| 221 | closing the gap between the mitral annulus and left PVs, except in 2 patients who had neither history |
| 222 | of mitral isthmus ablation nor low voltage areas on the mitral isthmus and 1 patient who had |
| 223 | complete mitral isthmus block at the beginning of the procedure. RF applications were performed |
| 224 | inside the CS in 12/34 patients. PMF was observed in 19 patients at the redo procedure (Figures 1B, |
| 225 | 2A). 15/19 (78.9%) showed recurrence of PMF with reconnection through the ablation line. |
| 226 | Although 4/19 (21.1%) patients showed a de novo PMF, the mitral isthmus gap was closed in the |
| 227 | first procedure despite the absence of clinically observed PMF. Occurrence of PMF in the first |
| 228 | procedure predicted the same AT circuit in the redo procedure with 78.9% sensitivity, 38.9% |
| 229 | specificity, 57.7% positive predictive value (PPV) and 63.6% negative predictive value (NPV). |
| 230 | The prevalence of RMAT in both first and redo procedures is summarized in Supplemental table 4. |
| 231 | RMAT was observed in 18 patients at the first procedure. Although 19 patients did not have a |
| 232 | clinical RMAT, the roof line was completed with bidirectional block closing the gap between the |

| 233 | right and left superior PVs, except in 2 patients who had neither history of RF applications nor low |
|-----|--|
| 234 | voltage areas on the roof. RMAT was observed in 10 patients at the redo procedure (Figure 1). 8/10 |
| 235 | (80.0%) showed recurrence of RMAT with reconnection through the ablation line, but 2/10 (20.0%) |
| 236 | showed a de novo RMAT. In these 2 patients the gap on the roof was closed during the first |
| 237 | procedure, although RMAT was not clinically observed. RMAT in the first procedure predicted the |
| 238 | same AT in the redo procedure with 80.0% sensitivity, 63.0% specificity, 44.4% PPV and 89.5% |
| 239 | NPV. |
| 240 | The prevalence of PTF in both first and redo procedures is summarized in Supplemental table 5. PTF |
| 241 | was observed in 10 patients at the first procedure; none showed recurrence of PTF but there was one |
| 242 | de novo PTF. PTF in the first procedure predicted the same AT with 0% sensitivity, 72.2% |
| 243 | specificity, 0% PPV and 96.3% NPV. |
| 244 | |
| 245 | Non-AMATs |
| 246 | The prevalence of Non-AMAT in both first and redo procedures were summarized in the |
| 247 | Supplemental table 6. In the first procedure, 15 Non-AMATs were identified in 14 patients; localized |
| 248 | reentry around anterior LA scar in 2, septal LA scar in 3, posterior LA scar in 2, mitral isthmus scar |
| 249 | in 2, LAA scar in 2, and right PV-related reentry in 3, and RA crista macroreentry in 1. In the redo |
| 250 | procedure, 12 Non-AMATs were observed in 12 patients. Although 5 of them had had Non-AMATs |

- at the first procedure, none of them showed recurrence of the same Non-AMAT circuit (Figure 1,
- 252 Figure 2B), except one biatrial AT rotating around the septal scar. 11 Non-AMATs were newly
- 253 observed in the redo procedure. Nine Non-AMATs were localized on the left atrium; around anterior
- LA in 2, around LAA-ridge scar in 6, and right PV gap related AT in 1. The remaining 1 involved
- 255 both LA and RA in the circuit. Circuits of newly developed Non-AMATs corresponded with low
- 256 voltage areas which were related to the previous ablation for AF and/or AT. Non-AMAT in the first
- 257 procedure predicted the Non-AMAT (but not the same Non-AMAT) with 41.7% sensitivity, 64.0%

specificity, 35.7% PPV and 69.6% NPV, although the most circuits were different between the first

and the redo procedure. In these 12 patients who had Non-AMAT at the redo procedure, 4 patients

260 showed coexistent AMATs during the procedure.

261

262 Focal ATs

- 263 The prevalence of focal AT in both first and redo procedures were summarized in the Supplemental
- table 7. In the first procedure, 5 focal ATs originating from the right PV, inferior LA, left lateral
- 265 ridge, left atrial appendage and septal LA were observed in 3 patients. In the redo procedure, 1 focal
- AT from the lateral RA was identified in 1 patient, who had not had focal AT at the first procedure.
- 267 Therefore, no patients developed recurrence of the same AT (Figure 1). The origin of new focal ATs
- 268 corresponded with areas ablated during previous AF ablation (Figure 2C). Absence of focal ATs at
- the first procedure predicted the absence of focal ATs at the second procedure with a NPV of 97.1%.
- 270

271 Incidence of ATs using epicardial structures

- ATs using epicardial structures were observed in 18/37 (48.6%) patients (Figure 3). Epicardial
- 273 structure related ATs were identified in 15/19 (79.0%) PMF (Figure 4A, Video 1), 3/10 (30.0%)
- 274 RMAT (Figure 4B, Video 2), and 4/12 (33.3%) Non-AMATs (Figure 4C, Video 3). In most cases,
- the structure used for the epicardial circuit was the CS/VOM system (n=16). However, 1
- 276 Non-AMAT circuit may have used both CS/VOM and Bachmann's bundle (Figure 4C), and this AT
- 277 converted to a PMF using Bachmann's bundle during the procedure. One circuit in a RMAT may
- 278 have solely used Bachmann's bundle.
- 279

280 Treatment and outcomes of the redo AT ablation procedure

- 281 In total, out of 18 patients with the circuit including epicardial structures, 6 (33.3%) patients had a
- 282 recurrent AT. In 16 patients with ATs related to the CS/VOM, 5 received the EI-VOM followed by

283 RF ablation and 11 had RF applications only. Five with RF treatment only, had another recurrence, and two of them received a 3rd procedure. One demonstrated multiple localized ATs around the LA 284 285 and RA septal scars and an epicardial reconnection on the mitral isthmus. AT was terminated by a 286 linear lesion from the septal scar to the right pulmonary vein lesions and the mitral isthmus was 287 blocked by EI-VOM. The other presented in sinus rhythm and unstable ATs were induced. EI-VOM 288 organized the unstable ATs to an anterior localized AT which was terminated by a linear lesion from 289 an anterior scar to the mitral annulus. 290 Among the remaining 2 patients, one patient with Bachmann's bundle related RMAT developed 291 multiple ATs associated with both left and right septal scar areas but complete block was preserved 292 on the roof. The other patient showed the localized reentrant AT which included both VOM and 293 Bachmann's bundle in the circuit (Figure 4C). EI-VOM changed the AT to PMF with conduction 294 through the Bachmann's bundle, and the PMF was terminated with the ablation on the gap of the 295 mitral isthmus. In total, 6 patients treated with EI-VOM during the redo procedure did not show any 296 recurrence, though 6/12 (50.0%) treated with RF showed AT recurrence (P=0.05). 297 298 Among 16 patients without epicardial structure-related ATs, 9 (56.3%) patients had AT recurrence,

and 6 of them received a 3rd AT procedure; 3 patients developed RMATs, two of which were around 299 300 the RPV and terminated with ablation on a roof gap, and the other was around the LPV using the 301 VOM and terminated by EI-VOM. One patient developed VOM-related PMF and anterior localized 302 AT, treated by EI-VOM and linear lesions from the anterior scar to the mitral annulus. One patient 303 demonstrated a localized septal AT, which was completed with a linear lesion from the septal scar to 304 the mitral annulus; and the remaining had only AF induced during the 3rd AT procedure. EI-VOM 305 and RPV re-isolation were performed and roof block was confirmed. No ATs were induced with 306 burst pacing under isoproterenol at the end of the procedure. 307

309 **DISCUSSION**

- 310
- 311 Major findings
- 312 This study demonstrates that:
- 313 1. Redo AT procedures offer the opportunity to quantify the true failure rate, ie reconnection of
- 314 previously blocked targets
- 315 2. PMF is the most common type of recurrence of the AFA-rAT. Redo AFA-rAT ablation
- 316 procedures demonstrated a true failure rate of 57.7%, followed by RMAT, with a true failure at
- 317 44.4%.
- 318 3. Epicardial structures were included in the circuit in 78.9% of PMF, 30.0% of RMATs, and 33.3%
- 319 of Non-AMATs. The very high true failure rate in PMF may be explained by the highest
- 320 involvement of epicardial structures.
- 321 4. The EI-VOM may be an option to prevent recurrence of PMF.
- 322 5. Non-AMATs (localized ATs) are frequent, both in the first and redo AT procedures, but the circuit
- 323 is usually different.
- 324 6. Information of ATs in the first procedure is useful to guide the redo procedure of AFA-rAT.
- 325

326 High-incidence of PMF

- 327 PMF provides the typical true failure of ablation, and this is likely related to the frequent
- 328 involvement of the CS/VOM epicardial structures. Regardless of the AT mechanism in the first
- 329 procedure, PMF should be considered when assessing the AT mechanism in the redo procedure.
- 330 Additionally, when PMF is observed in the first procedure, the same AT may be identified in the

| 332 | first procedure in the study population, patients frequently developed recurrence. This highlights the |
|-----|--|
| 333 | difficulty in creating durable lesions on the mitral isthmus. |
| 334 | This may at least in part be due to anatomical limitations: a thicker and longer mitral isthmus and the |
| 335 | presence of an anatomical pouch (20%) may make it difficult to create contiguous and transmural |
| 336 | linear lesions ^{15,16} . The circumflex artery, which is interposed between the mitral isthmus and the CS |
| 337 | in 35%, predicts the failure of mitral isthmus block ¹⁷ . The heat sink effect of blood flow in the |
| 338 | circumflex artery may prevent adequate heating of the atrial myocardium at the mitral isthmus |
| 339 | during both endocardial and epicardial RF energy delivery. |
| 340 | Half of the study population had long-standing persistent AF as their original AF type, and 78% of |
| 341 | them had severe LA dilation. This challenging patient population, as well as additional factors such |
| 342 | as the absence of contact force or use of systemic drug challenge (adenosine or isoproterenol) during |
| 343 | the procedure may also lead to a higher recurrence rate. However, we should emphasize the |
| 344 | important anatomical features in this region, with epicardial structures such as the CS and VOM |
| 345 | possibly bypassing the endocardial activation as mentioned below. To achieve the higher success |
| 346 | rate, not only the accurate diagnosis of the AT circuits, but also transmural and durable lesions |
| 347 | should be created in this specific region. |
| 348 | |

redo AT procedure in 60% of patients. Although bidirectional block was confirmed at the end of the

349 Importance of considering epicardial structures as a target

350 The present study demonstrated that epicardial structures were included in the circuit in 78.9% of 351 PMF, 30.0% of RMATs, and 33.3% of Non-AMATs. The most well-known epicardial structures 352 associated with ATs are the CS and the VOM. The VOM is the most consistent LA vein and is found in 84%-99%^{18,19}, with a mean length of 2-3 cm and an average diameter of 1mm. Valderrábano M et 353 al successfully cannulated the VOM in 86.2% of cases.²⁰ Despite its consistent presence, the VOM 354 355 varies significantly in size, branching patterns, and capillary content. 356 PMF recurrence due to residual conduction in epicardial structures regardless of the endocardial block has been previously reported^{21,22} and may be under-diagnosed due to anatomical variety and 357 358 the lower resolution of previous mapping systems. It may commonly be difficult to affect epicardial 359 conduction through endocardial ablation. Although it is difficult to provide direct RF application in the VOM because it is usually too small, ethanol-injection may be an useful alternative²³. The 360 361 present study showed that AT recurrence in VOM/CS related ATs was observed in 5/11 (37.5%) 362 treated with ablation only and 0/6 (0%) treated with EI-VOM (P=0.10). Although the difference did 363 not reach significance because of the small number of cases, EI-VOM may be an additional option to 364 achieve durable lesions on the mitral isthmus. Although septal line or anterior line may be the other 365 options to treat the PMF, these lines should be chosen carefully; these lines may not only lead to the disturbance of a normal activation during sinus rhythm, but also result in biatrial tachycardias^{4,24}. 366 Another contributing epicardial structure is Bachmann's bundle²⁵⁻²⁷. Muscle fascicles of Bachmann's 367 368 bundle originate near the sinoatrial node, extending leftward, joined by another muscle bundle 369 originated from the lateral RA wall, and passes inferior to the region of the sinoatrial node. After 370 traversing the interatrial groove, Bachmann's bundle advances leftward over the antero-superior part 371 of the LA, where it branches, encircling the orifice of the LAA, finally fusing on the lateral wall of the LA, progressing to the posterior LA wall.²⁷ Other interatrial connections between RA and LA are 372 373 also present²⁷, including bundles at the posterior side of the interatrial septum and a septopulmonary

| 374 | bundle, and a posterosuperior bundle which originates from the obliquely directed atrial myocardium |
|-----|--|
| 375 | of the posterior RA wall or the superior vena cava ²⁷ . Fibrosis, anisotropic fiber orientation, |
| 376 | slow/preferential conduction, and supernormal excitability have been reported for Bachmann's |
| 377 | bundle in vitro and in animals—all of which can facilitate epicardial reentry. ²⁸ The diagnosis and |
| 378 | treatment of Bachmann's bundle related AT may be more difficult due to the difficulty in directly |
| 379 | mapping and ablating this structure. Additional epicardial ablation may be useful to complete |
| 380 | transmural lesions through endo-to-epi cardium and required for the difficult cohort of AFA-rAT. ²⁹ |
| 381 | |
| 382 | Clinical Implications |
| 383 | We describe mechanisms of recurrence of organized ATs post AF ablation, comparing first vs. redo |

384 procedures. Despite high-resolution and high-density mapping with the RhythmiaTM mapping system,

385 recurrence is high at the roof and perimitral regions, and that different non-AMATs also recur.

386 Depending on the ATs observed in the first procedure, recurrent ATs in the redo AT procedure

387 showed specific patterns. Additionally, in the redo AT procedure, recurrent ATs, especially PMF,

388 frequently included epicardial structures in their circuits. Not only the CS and VOM, but also

389 Bachmann's bundle, are important structures which can bypass endocardial activation.

390

391 Limitations

Firstly, the main limitation of the present study is the small sample size, which limited most of the statistical analyses to frequency and percent summaries. Second, the findings in this study may not be generalized to AFA-rAT patients only having undergone PV-isolation, as atypical atrial flutter with different types of reentry circuits may be secondary to the extensive ablation undertaken in the first or previous multiple ablation sessions, or additionally from progressive remodeling. In fact,

| 397 | most patients in this study originally had persistent AF and long-standing persistent AF, and the LA |
|-----|--|
| 398 | volume at the first procedure was relatively large. Such an extensive AF ablation strategy is being |
| 399 | used less frequently currently and so the observations of this study may not be as relevant in the |
| 400 | current era of AF ablation. Third, although patients included in the present study all had documented |
| 401 | ATs, some patients presented with SR at the beginning of the procedure. In these patients, induced |
| 402 | ATs might have matched the documented AT. However, it is often difficult to discern this from the |
| 403 | P-wave morphology alone as usually the P-wave is small in these patients with extensively damaged |
| 404 | atrium due to previous ablations and remodeling. Fourth, endocardial mapping systems, whatever |
| 405 | their resolution, are unable to collect epicardial activation mapping data; therefore, even though the |
| 406 | involvement of epicardial structures was highly suggestive based on anatomical and |
| 407 | electrophysiological information of other sites on the circuit, it was not confirmed directly. 9,18,19,23,25 |
| 408 | However, for example, the termination of the AT with ablation on the ridge or ethanol-infusion in |
| 409 | the VOM strongly suggests the involvement of CS/VOM system. ^{9,18,19,23,25} Finally, some patients |
| 410 | developed PMF or RMAT at the redo procedure even though these ATs were not identified in the |
| 411 | first procedure. Although these may have occurred because of RF applications to close the gap in a |
| 412 | low voltage area seen during the first procedure, it is difficult to determine whether these anatomical |
| 413 | gaps can be left when a clinical AT is not observed. A prospective study is needed to elucidate this. |
| 414 | |

415 CONCLUSION

| 422 | optional treatment. |
|-----|---|
| 421 | developed recurrent ATs related to epicardial structures, and ethanol-infusion in the VOM may be an |
| 420 | when it is identified in the first session, the circuit may be different. Approximately 60% of patients |
| 419 | present in the redo AT procedure. Although Non-AMAT may be possible in the redo procedure |
| 418 | in the first procedure with the Rhythmia TM mapping systen, these ATs were highly unlikely to be |
| 417 | regardless of the prior procedures. When RMAT, CTI-dependent AT or focal AT was not identified |
| 416 | PMF should be frequently considered in the mechanism of recurrence after ablation of AFA-rAT, |

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534 Table 1. Patient demographics

| | N=37 |
|---|--------------|
| Age at the redo AT procedure | |
| Age at the first AT procedure, y | 62.3+/-8.8 |
| Female | 8 (21.6%) |
| SHD | 7 (18.9%) |
| Persistent AF as an original AF type | 37 (100%) |
| Longstanding (>12months) | 18 (48.6%) |
| Persistent (<12months) | 19 (51.4%) |
| Post-Cardiac surgery | 2 (5.4%) |
| AF Ablation before the first AT procedure | 37 (100%) |
| PVI | 37 (100%) |
| LA defragmentation | 28 (75.7%) |
| Roof line | 15 (40.5%) |
| Mitral isthmus line | 17 (45.9%) |
| CTI line | 28 (75.7%) |
| lo of procedures | 2.6+/-1.0 |
| 1 procedure before the first AT procedure | 0 17 (45.9%) |
| >2 procedures before the first AT procedure | 20 (54.1%) |
| Prior ablation for AT with different mapping ystem | 18 (48.6%) |
| CHF | 1 (2.7%) |
| IT in tiat at | 16 (43.2%) |
| DM | 0 (0%) |
| troke | 3 (8.1%) |
| miodarone | 21 (56.8%) |
| CHA ₂ DS ₂ -VASc ₂ score | 1.3+/-1.2 |
| LVEF, % | 56.6+/-9.2 |
- 536 AF, atrial fibrillation; AT, atrial tachycardia; CHF, congestive heart failure; CTI, cavo-tricuspid
- 537 isthmus; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; PVI,
- 538 pulmonary vein isolation; SHD, structural heart disease

Dischaitmential, and not to be further dischosed.

539 Table 2. Mapping data

| | N=37 |
|--------------------------------------|--------------|
| Rhythm on the arrival at the EP lab | |
| SR | 9 (24.3%) |
| AT | 28 (75.7%) |
| AF | 0 (0%) |
| LA mapping points | 16229+/-8222 |
| LA mapping time | 1108+/-512 |
| LAV, ml | 152+/-32 |
| LAV (>150ml) | 18 (48.6%) |
| LAV (>200ml) | 2 (5.4%) |
| LAVI, ml/m2 | 52.8+/-18.7 |
| Severe LA enlargement (LAVI≥40ml/m2) | 29 (78.4%) |

540 AF, atrial fibrillation; AT, atrial tachycardia, LA, left atrium; LAV, left atrial volume; LAVI, left

541 atrial volume first; SR, sinus rhythm

| Table 3. | | AT in the first AT in the redo | | Durchurg | |
|----------|---------------------------|----------------------------------|-----------------------------|------------------------|--|
| | | procedure | procedure | P values | |
| Total A | AT | 68 | 43 | N° es | |
| Foca | al AT | 5 (7.4%) | 1 (2.3%) | 0.4 | |
| AM | AT | 48 (70.6%) | 30 (69.8%) | ð. 1 | |
| P | MF | 23 (33.8%) | 19 (44.2%) | 0.32 | |
| R | MAT | 15 (22.1%) | 10 (23.3%) | 1 | |
| P | TF | 10 (14.7%) | 1 (2.3%) | 0.05 | |
| Non | -AMAT | 15 (22.1%) | 12 (27.9%) | 0.5 | |
| 545 | | Thetennot | | | |
| 546 | AMAT, anatomical mac | croreentrant atrial tachycardia; | AT, atrial tachycardia; PMI | F, perimitral flutter; | |
| 547 | PTF, peritricuspid flutte | r; RMAT, roof-dependent mac | roreentrant AT | | |
| 548 | | | | | |
| 549 | Table 4. Comparison o | f patient between the first an | d redo procedure | | |
| | | AT in t | he first | AT in the redo | |
| | | proce | edure | procedure | |
| | | | | | |

544 Table 3. Comparison of AT between the first and redo procedures

| Focal AT | 3 (8.1%) | 1 (2.7%) |
|----------|------------|------------|
| AMAT | 35 (94.6%) | 27 (73.0%) |
| PMF | 26 (70.3%) | 19 (51.4%) |
| RMAT | 18 (48.6%) | 10 (27.0%) |
| PTF | 10 (27.0%) | 1 (2.7%) |
| Non-AMAT | 14 (37.8%) | 12 (32.4%) |
| | 6 18 | 5 |

551 AMAT, anatomical macroreentrant atrial tachycardia; AT, atrial tachycardia; PMF, perimitral flutter;

552 PTF, peritricuspid flutter; RMAT, roof-dependent macroreentrant AT

| ~ | - | 4 |
|---|---|----|
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| 2 | 2 | т. |

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| | | | | | | |

| 557 Figure 1. The incidence of the same AT circuit b | between the first and redo procedures. |
|--|--|
|--|--|

558 (A)Based on the AT at the first procedure (B) Based on the AT at the redo procedure

559

560 Figure 2: AT circuit at the second AT procedure

561 A. Peri-mitral flutter

- 562 The first procedure demonstrated peri-mitral flutter (CL=240ms) with line of block on the roof (i).
- 563 After wide circumferential reisolation of the pulmonary veins, ablation on the mitral isthmus
- 564 terminated the AT and ended up with a bi-directional block. The redo AT procedure demonstrated
- 565 the same peri-mitral flutter (CL=402ms) using a tiny gap at the inferior lip of the left inferior
- 566 pulmonary vein, which was blocked with additional application on the mitral isthmus (ii). Significant
- 567 elongation of the CL in the same circuit may be explained by extensive slow conduction at the gap.

568 B. Non-AMAT

- 569 In the first procedure, AT1 was a Non-AMAT (left panel, Figure 2A) turning around the anterior
- 570 scar, which converted to peri-mitral flutter (AT2, right panel, Figure 2A) with two RF applications at
- 571 the gap between the anterior scar and LAA scar (i). AT2 terminated by a linear lesion on the mitral
- 572 isthmus with bidirectional block at the end of the procedure. The recurrent AT was a different
- 573 Non-AMAT around the LAA with a line of block at the previously ablated region (black tags) (ii).
- 574 The AT terminated by linear lesions between the LAA ostial scar and the LSPV scar.

575 C. Focal AT

- 576 Extensive ablation including defragmentation and linear lesions in both right and left atria had been
- 577 performed in the previous two AF ablation procedures. The first procedure for the AFA-rAT

- 578 demonstrated a peritricuspid AT which terminated with linear lesions on the CTI. Extensive low
- 579 voltage regions were observed in the RA (i). The recurrent AT was a focal AT originating from the
- 580 border of this scar area (white circle) (ii).
- 581 Figure 3. Incidence of ATs using epicardial structures
- 582 Figure 4: Recurrent ATs using epicardial structures in their circuits
- 583 A. Perimital flutter using epicardial structures
- 584 The first AT was a peri-mitral flutter, which terminated by a linear lesion on the mitral isthmus with
- 585 bidirectional block at the end of the procedure. The recurrent AT (CL=275ms) showed a centrifugal
- 586 pattern from the top of the ridge close to the LAA ostium (Video 1). Entrainment mapping
- 587 demonstrated a reentrant, as opposed to focal, mechanism, with a circuit around the mitral annulus
- 588 despite the endocardial block on the mitral isthmus, probably bypassed by the VOM. The AT
- 589 terminated with ethanol-infusion in the VOM.

590 B. RMAT using epicardial structures

- 591 The first procedure involved a RMAT, which terminated by a linear lesion on the LA roof with
- 592 bidirectional block at the end of the procedure. The recurrent AT (CL=210ms) showed a centrifugal
- 593 pattern from the posterior LA (Video 2). However, entrainment mapping proved that the AT was not
- 594 focal AT but a RMAT around both pulmonary veins. The roof was endocardially blocked but
- 595 epicardial conduction remained through the posterior LA probably using Bachmann's bundle (dotted

596 line). The AT terminated with RF applications on the breakout point from this epicardial structure to

597 the endocardial LA (grey dots).

598 C. Non-AMAT using epicardial structures.

- 599 The first procedure included ablation of a localized right atrial AT, a focal septal AT, and a RMAT.
- 600 The recurrent AT (CL=232ms) showed a centrifugal pattern from the site anterior to the roof (Video
- 601 3). However, entrainment mapping proved that the AT was not focal AT but localized reentry around
- 602 the left atrial appendage, probably using two epicardial structures: the Ligament of Marshall from the
- 603 top to the bottom of the ridge (yellow dotted line), and Bachmann's bundle from its entrance anterior
- 604 to the LA to its exit anterior to the roof (white dotted line). Ethanol-infusion of the Vein of Marshall
- 605 converted this AT to a peri-mitral flutter using Bachmann's bundle, which terminated by linear
- 606 ablation on the mitral isthmus. Sclamontial, in
- 607



(A)

















AT at the second procedure







1694 5-7. A simple mechanism underlying the behavior of reentrant atrial tachycardia during

1695 ablation

1696

1697 Background and purpose of the study

In treating complex ATs, sometimes the AT terminates or changes to another AT contrary to our expectations. We hypothesize that, in the case of an index AT directly changing to another AT with a slower cycle length, there may be some rules that AT changes rather than de-novo initiation of the second AT. As the 'Rhythmia^{TM'} provides extremely high-resolution/high-density maps, it allows us to understand a precise circuit of the tachycardia. Using this system, we aimed to examine the mechanism of termination or conversion from one AT to a second AT, and to create an

algorithm to predict behaviors of AT on RF application.

1704 Methods and results

1705 From the analysis of a retrospective 101 consecutive reentrant ATs in 60 patients treated with the RhythmiaTM

- 1706 mapping system, we elucidated the relationship between the index AT circuit, ablation site, behavior of the AT during
- 1707 RF application, and subsequent AT circuit, then a simple algorism was created as shown in Figure 5-7. We
- 1708 prospectively applied this algorithm to 172 consecutive ATs, and demonstrated the accuracy of the algorithm.
- 1709



Figure 5-7. Algorithm to predict the behavior of AT during ablation

Algorithm workflow

1. Identify the region of wavefront collision (a).

2. Define the N or N-1 beat for each collided wavefront based on the ablation site (b)(c)

3. The wavefront generated from the distal region to the ablation site is defined as the N beat, and the wavefront originated from the proximal region to the ablation site is defined as the N-1 beat.

4. Collision between N-1/N-1 (or N/N) beats \rightarrow AT termination (b)

5. Collision between N/N-1 beats \rightarrow AT conversion (c)(d)



1712

- 1713 Accuracy to predict AT termination/conversion and the second AT circuit was 95.9% overall, 96.1% in AMATs,
- 1714 95.5% in non-AMATs and 95.7% in multiple-loop ATs. Prediction failure occurred in 8 ATs; either the second AT
- 1715 used an unmapped chamber or structure in the index map (n=7) or a line of block was misinterpreted as very slow
- 1716 conduction in the index map (n=1).
- 1717 Summary and conclusion

| 1718 | We describe a simple mechanism underlying the behavior of AT during ablation, and an algorithm that predicts the |
|------|--|
| 1719 | termination and conversion of ATs on RF application. The path of subsequent AT circuits may be predicted, which |
| 1720 | may enable ablation without remapping the entire chamber in combination with entrainment mapping. Knowing this |
| 1721 | information could help the operator to modify the strategy and to select the most effective ablation line that will take |
| 1722 | both the active and the possible passive circuit. This could result in higher termination rate, fewer RF deliveries, and |
| 1723 | shorter ablation procedures, although this needs further study. Our findings also may lead us to rethink the initial AF |
| 1724 | procedural strategy, as each ablation region may become a potential obstacle or slow-conduction area to cause N/N- |
| 1725 | 1 collision, resulting in potential future iatrogenic ATs. |
| 1726 | |
| 1727 | |
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| 1733 | Frontera A, Thompson N, Massoullié G, Wolf M, Duchateau J, Klotz N, Pambrun T, Sacher F, Cochet H, Hocini M, |
| 1734 | Haïssaguerre M, Jaïs P. |
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A simple mechanism underlying the behavior of reentrant atrial tachycardia during ablation @ O



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BACKGROUND Ablation of complex atrial tachycardias (ATs) is difficult.

OBJECTIVE The purpose of this study was to elucidate a mechanism underlying the behavior of ATs during ablation and to create an algorithm to predict it.

METHODS An algorithm predicting termination/conversion of AT and the second AT circuit associated with the ablation site was developed from 52 index reentrant AT high-resolution activation maps in 45 patients (retrospective phase). First, the wavefront collision site was identified. Then, the N or N-1 beat was defined for each collision associated with the ablation site. When the AT involved wavefront collision solely between N-1/N-1 (N/N) beats, the AT would terminate during ablation. Conversely, when the AT included wavefront collision between N/N-1 beats, the index AT would convert to a second AT. The algorithm was then prospectively tested in 172 patients with 194 ATs (127 anatomic macroreentrant ATs [AMATs], 44 non-AMATs, 23 multiple-loop ATs).

RESULTS Accuracy in predicting AT termination/conversion and the second AT circuit was 95.9% overall, 96.1% in AMATs, 95.5% in non-AMATs, and 95.7% in multiple-loop ATs. Median (25th–75th percentile) absolute variation between predicted and actually observed cycle length of the second AT was 6 (4–9) ms. Prediction failure occurred in 8 ATs; either the second AT used an unmapped chamber or structure in the index map (n = 7) or a line of block was misinterpreted as very slow conduction in the index map (n = 1).

CONCLUSION A simple mechanism underlies the behavior of ATs during ablation, even in complex ATs. With a simple algorithm using high-resolution mapping, AT termination/conversion and the second AT circuit and cycle length may be predicted from the index activation map.

KEYWORDS Catheter ablation; High-resolution mapping system; Multiple loop atrial tachycardia; Reentrant tachycardia

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incidence of iatrogenic atrial tachycardias (ATs), particularly those demonstrating complex mechanisms and anatomic cir-

cuits.1-5 A high-resolution mapping system allows mapping

Introduction

With the development of extensive substrate catheter and surgical ablation strategies for treatment of persistent atrial fibrillation (AF) has come a concurrent increase in the

This research was partially funded by a grant from 'Investissement d'avenir': IHU LIRYC ANR-10-IAHU-04. Drs Haïssaguerre, Hocini, Jaïs, and Sacher have received lecture fees from Biosense Webster and Abbott. Drs Denis, Derval, Jaïs, and Sacher received speaking honoraria and consulting fees from Boston Scientific. Drs Takigawa and Derval contributed equally to this study. Address reprint requests and correspondence: Dr Masateru Takigawa, Bordeaux University Hospital, Avenue de Magellan, 33600, Pessac, France, E-mail address: teru.takigawa@gmail.com. with sufficient resolution to demonstrate the precise activation sequence of ATs.²⁻⁴ With such a system, precise and complete activation characteristics of the atrium can be displayed.⁶ When treating complex ATs, the AT may terminate or change to another AT, contrary to our expectations. We hypothesize that, in the case of an index AT that directly changes to another AT with a slower cycle length (CL), there may be a simple mechanism to unmask this rather than *de novo* initiation of the second AT. The purpose of this study was to examine the mechanism of termination or conversion

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from one AT to a second AT using a high-resolution mapping system and to create an algorithm to predict behaviors of AT upon radiofrequency (RF) application.

Methods

Creation of the algorithm from retrospective data

We retrospectively analyzed 60 consecutive patients with reentrant ATs mapped using the Rhythmia system (Boston Scientific, Marlborough, MA) between 2014 and 2015. ATs with a complete index map in which the specific RF application resulted in termination of AT or conversion to the second AT with a complete activation map were analyzed, and the association between the ablation site and the reaction (termination of AT or change of CL/activation pattern) to the RF application was examined. Of 101 consecutive reentrant ATs in these 60 patients, the relationship between the index AT circuit, ablation site, behavior of the AT during RF application, and subsequent AT circuit was evident in 52 reentrant ATs in 45 patients (Supplemental Table 1). These index ATs, which with RF application either terminated directly to sinus rhythm (n = 47) or converted to a second AT (n = 5), were used to develop the following algorithm. In the case of a change in activation or CL of the AT, the subsequent second AT circuit was also analyzed to examine the relationship to the index AT circuit.

Algorithm

From the retrospective series, we developed a straightforward algorithm to predict termination/conversion of the AT and the circuit of any subsequent ATs (Figure 1). The brief flow of the algorithm is as follows:

- 1. Identify the region of wavefront collision.
- 2. Define the N or N-1 beat for each collided wavefront associated with the ablation site, which is clinically decided by the operator. Based on the ablation site, the wavefront generated from the distal region to the ablation site is defined as the N beat, and the wavefront originated from the proximal region to the ablation site is defined as the N-1 beat.
 - When the AT involves wavefront collision between N-1/N-1 (or N/N) beats, the AT will terminate during ablation.
 - When the AT involves wavefront collision between N/N-1 beats, the index AT will convert to a second AT, using a common path of the index AT. The AT CL can also be predicted from the index AT (Figure 2).

Electrophysiological study and mapping with Rhythmia

Electrophysiological study and mapping with the Rhythmia system were performed as previously described.^{2–4,6} Antiarrhythmic medications were discontinued >5 half-lives before ablation, except for amiodarone. A steerable decapolar catheter was introduced within the coronary sinus.

If patients were in sinus rhythm at the beginning of the procedure, AT was induced with burst pacing regardless of reconduction or block of previous pulmonary vein (PV) or linear lesions. ATs were mapped with the Orion multipolar basket catheter and Rhythmia system (Boston Scientific) with support from a steerable long sheath (Agilis, Abbott, MN; Zurpaz, Boston Scientific, Marlborough, MA). An activation map was created under standard automatic beat acceptance criteria based on (1) CL variation; (2) activation time difference variations between the coronary sinus electrograms; (3) catheter motion; (4) electrogram stability; (5) catheter tracking quality; and (6) respiration gating. Although the dense scar threshold was nominally set at 0.03 mV as a confidence mask parameter, it was manually lowered to be as close as possible to the noise threshold, to allow visualization of the entire circuit.^{2–4}

Definition of AT

We classified AT according to the activation pattern: focal AT, anatomic macroreentrant AT (AMAT), and non-AMAT (localized reentry). As previously reported,^{2,7} AMATs included peritricuspid AT dependent on the cavotricuspid isthmus, perimitral AT dependent on the mitral isthmus, and roof-dependent AT dependent on the left atrial (LA) roof. Others were all defined as non-AMAT. Multiple-loop ATs were defined as those composed of >1 in-dependent active circuit sharing 1 common isthmus, including dual-loop ATs and triple-loop ATs, with the entire CL included in each of the circuits. After the activation map was completed, entrainment pacing was performed to confirm the diagnosis unless there were unstable ATs or ATs with short CL (<200 ms), for which entrainment pacing might result in conversion or termination of the index AT.

Catheter ablation

After diagnosis of the AT circuit from activation and entrainment mapping, the appropriate ablation site was determined based on anatomic length, catheter stability, tissue thickness, and nearby vulnerable structures. In most cases, this represented the narrowest bridge of conducting tissue between scars or anatomic obstacles. The endpoint for ablation, irrespective of the type of isthmus selected, was achievement of bidirectional conduction block.^{8–11} PVs were reisolated when needed. RF energy was delivered using an irrigated 3.5-mm-tip ablation catheter (ThermoCool SF catheter, Biosense Webster, Diamond Bar, CA), with power of 30–40 W and cutoff temperature of 45°C.

Prospective validation of the algorithm

The algorithm was tested prospectively in 172 consecutive AT patients undergoing RF catheter ablation to assess its accuracy in predicting AT behavior with ablation and relationship to the subsequent AT. In the prospective phase, the following ATs were excluded from the analysis:

- 1. Index AT = focal AT
- Unknown relationship between the index AT and RF application:



Figure 1 Algorithm for predicting atrial tachycardia (AT) behavior during ablation. A: Index AT circuit around anterior scar (I) and a passive secondary circuit around the mitral valve (S). B: When the lateral line between the mitral valve (MV) and left pulmonary vein (LPV) scar is chosen as an ablation site, the last activation front rotating around the anterior scar "I (N)" collides with the previous wavefront rotating around the MV "S (N-1)." C: As a result, when the lateral lesion is completed, "S (N-1)" will not meet "I (N)," resulting in the second passive circuit around the MV becoming the index circuit. D: When the anterior line between the MV and the anterior scar is chosen as an ablation site, the last activation wavefront rotating around the anterior scar "I (N-1)" cilides with the lateral lesion is completed, "S (N-1)" will not meet "I (N)," resulting in the second passive circuit around the MV becoming the index circuit. D: When the anterior line between the MV and the anterior scar is chosen as an ablation site, the last activation wavefront rotating around the anterior scar "I (N-1)" cilides with the lateral activation wavefront rotating around the MV "S (N-1)," cilides with the lateral activation wavefront rotating around the anterior scar "I (N-1)" collides with the lateral activation wavefront rotating around the MV "S (N-1)," cilides with the lateral activation wavefront rotating around the MV "S (N-1)," cilides with the lateral activation wavefront rotating around the MV "S (N-1)," resulting in AT termination when the next wavefront is blocked at the ablation lesion. RPV = right pulmonary vein.

- A. Termination/conversion of the index AT without ablation
- B. Unclear circuit despite a complete activation map of the index AT
- C. Termination/conversion of the second AT before a complete activation map
- 3. Ablation failure of the index AT

In the prospective phase, after the operator had determined the ablation site from activation and entrainment mapping, the impact of RF application (termination/conversion of the AT) and the subsequent AT circuit were predicted in real time by an investigator (Investigator 1) before ablation, using the algorithm created from the retrospective data. The operator was blinded from the prediction using the algorithm. AT conversion was defined as the point when the sequence or CL in the coronary sinus changed directly from the index AT on ablation. When the index AT converted to a second AT during RF application, the originally planned linear line between scar or anatomic obstacles was completed before the second AT activation map was created. However, when the common isthmus of a multiple-loop AT was not targeted and instead a specific isthmus for 1 loop was ablated, the endpoint of linear ablation for the index AT was left at the operator's discretion, as in this case the activation pattern or CL in the CS might not change, even if the targeted circuit was transected.

To assess the reproducibility of this algorithm, another investigator (Investigator 2), who was blinded to the outcome of RF application, predicted the behavior of the AT offline with information from the activation map of the index AT and the ablated site. The predicted result was then compared to that performed in real time during the procedure by Investigator 1.

All patients gave written informed consent according to the institutional guidelines of the University of Bordeaux Health System, which provided ethical approval for the study.

Statistical analysis

Data are given as mean \pm SD or median (25th–75th percentile) for continuous variables and as percentages for frequencies. To compare groups, χ^2 analysis or the Fisher exact test was used for categorical variables, and analysis of variance or the Kruskal–Wallis test was used for continuous variables. *P* <.05 was considered significant. Interobserver agreement for the prediction of AT behavior following the algorithm was evaluated by calculating the Cohen kappa coefficient.



Figure 2 Prediction of the atrial tachycardia cycle length (ATCL) of the second AT. The CL of the second AT can be predicted from the index AT map. The second ATCL is slower than the index ATCL by the timing between the time the wavefront splits from the index AT and when the wavefront of N/N-1 collides in the second AT circuit.

Results

Validation of the algorithm in prospective series

To validate the accuracy of the algorithm, 273 ATs in 172 patients were prospectively examined. A total of 79 index ATs were excluded. Therefore, 194 ATs in 130 patients (Table 1 and Figure 3) were analyzed for the validation analysis, which included 127 AMATs, 44 non-AMAT (localized AT), and 23 multiple-loop ATs.

Thirty-nine ATs were predicted to convert; of these, 38 (97.4%) did convert to a subsequent AT and 1 (2.6%) terminated. Figure 4A (Supplemental Video 1), Figure 4B (Supplemental Video 2), and Supplemental Figure 1 show 3 examples of circuits for which behavior on RF application was accurately predicted.

Termination with RF was predicted in 155 ATs; of these, 148 (95.5%) terminated and 7 (4.5%) converted to a second AT. Of the 148 ATs that terminated, a second map was created in 7 (4.7%) because the ATCL stabilized with a slower CL during ablation. However, the activation map generally demonstrated the same circuit but with slower conduction or a similar circuit using the gap at the ablated region, which was finally transected by further ablation with higher output and better contact in the same region as planned from the beginning of the RF application (Supplemental Figure 2).

Results by tachycardia type

Among 127 AMATs (18 peritricuspid AT, 62 perimitral ATs, 47 roof-dependent ATs), termination was predicted in 112 (88.2%). Of these 112 ATs, 5 (4.5%) converted to a second AT. Of the converted ATs, 3 of these changed from an LA AT to a peritricuspid AT, and the other 2 converted to ATs using an epicardial circuit. Fifteen ATs were predicted to convert to AMATs, and all did convert to a second AT, with a circuit correctly predicted from the index AT (Figure 4A and Supplemental Video 1).

Termination was predicted in 30 of 44 non-AMATs (68.2%). Of these 30, 1 (3.3%) converted from an LA AT to a right atrial AT. Conversion was predicted in 14 ATs, and 13 of the 14 (92.9%) did convert to a second AT, with a circuit predicted from the index AT (Figure 4B and Supplemental Video 2), including 9 AMATs, 4 non-AMATs, and 1

dual-loop. In the remaining non-AMAT, the location associated with N-1/N collision that was thought to be very slow conduction was actually blocked completely (Supplemental Figure 3).

Termination was predicted in 13 of 23 multiple-loop ATs (56.5%). Of these 13 ATs, 1 (7.7%) converted from an LA AT to a peritricuspid AT. Conversion was predicted in 11 multiple-loop ATs, and all did convert to a second AT, with a circuit predicted from the index AT (Supplemental Figure 1). These were all AMATs.

Accuracy of the algorithm

Overall, the algorithm predicted termination and conversion to a subsequent AT and its circuit with 95.9% accuracy

| Table 1 | Patient demographics from the prospective series |
|-----------|--|
| (N = 130) | |

| Age (vrs) | 61.6 + 10.9 |
|-----------------------------|-----------------|
| Female | 37 (28 5) |
| SHD | 37 (28.5) |
| Valuular heart disease | 16 (12 2) |
| Connected Lineare | 10 (12.3) |
| Congenitat neart disease | 9 (6.9) |
| Ischemic heart disease | 2 (1.5) |
| Hypertrophic cardiomyopathy | 6 (4.6) |
| Idiopathic | 5 (3.8) |
| Postprocedure | |
| Postcardiovascular surgery | 19 (14.6) |
| Post-AF ablation | 107 (82.3) |
| PVI | 107 (82.3) |
| LA defragmentation | 79 (60.8) |
| Roof line | 62 (47.7) |
| Mitral isthmus line | 64 (49.2) |
| CTI line | 80 (61.5) |
| No. of procedures | 2.7 ± 1.3 |
| CHF | 25 (19.2) |
| HT | 55 (42.3) |
| DM | 6 (4.6) |
| Stroke | 4 (3.1) |
| CHA2DS2-VASc2 score | 1.5 ± 1.2 |
| LVEF (%) | 54.1 ± 10.8 |

Values are given as mean \pm SD or n (%)

 $\label{eq:AF} \begin{array}{l} \mathsf{AF} = \mathsf{atrial fibrillation; CHF} = \mathsf{congestive heart failure; CTI} = \mathsf{cavotricus-pid} is thmus; DM = \mathsf{diabetes mellitus; HT} = \mathsf{hypertension; LA} = \mathsf{left atrium; LVEF} = \mathsf{left ventricular ejection fraction; PVI} = \mathsf{pulmonary vein isolation; SHD} = \mathsf{structural heart disease.} \end{array}$



Figure 3 Flowchart and result of prediction in the prospective phase. *LA AMATs converted to 3 peritricuspid ATs and 2 VOM-related AT. †LA non-AMAT converted to RA AT. ‡LA multiple-loop AT converted to peritricuspid AT. §LA non-AMAT terminated because of misinterpretation between slow conduction vs complete block. AMAT = anatomic macroreentrant atrial tachycardia; AT = atrial tachycardia; LA = left atrium; RA = right atrium; VOM = vein of Marshall.

(Table 2). The Cohen kappa coefficient for interobserver agreement in predicting AT behavior during RF application was 0.97 (95% confidence interval 0.83–1.11).

Tachycardia CL in index and subsequent ATs

Median CL of the second AT that converted directly from the index AT during ablation was longer than that of the index AT [289 (248–348) ms vs 249 (224–298) ms, respectively; P < .0001] (Table 3). The absolute difference between predicted and observed CL of the second AT was 6 (4–9) ms and was \leq 10 ms in 32 of 38 ATs (84.2%).

Discussion

Major findings

This study demonstrated that (1) the behavior of AT during RF application simply depends on wavefront collision and ablation sites; (2) not only the impact (termination or conversion) of RF application but also the circuit and CL of the subsequent AT may be predicted, and ultra-high-resolution mapping system is helpful in this prediction; and (3) prediction failures are rarely observed and are the result of unmapped/unmappable chambers or structures, misinterpretation between complete block and very slow conduction, and AT slowing without change in the circuit.

Mechanism of AT conversion

In our series, we demonstrated that all second ATs that directly convert from an index AT were masked while the index AT was still running. The continuation of a tachycardia as a second AT that was present during the index AT but concealed by virtue of being entrained is shown in Figure 2. Although it is theoretically possible that an automatic focal tachycardia might be overdriven, we did not encounter this in our series.

While the faster index AT is running, the index AT is repetitively resetting the second longer circuit in each beat. The second AT will continue when the index AT terminates as there will be no antidromic wavefront with which to collide; thus, the second tachycardia wavefront will proceed uninterrupted through the reentrant circuit at its original rate. This concept was demonstrated with conventional entrainment maneuvers in a simple AMAT in a previous study.¹² However, using high-resolution mapping, we succeeded in demonstrating that this concept still applies in complex ATs, and the behavior of AT during ablation, the circuit, and the CL of the second AT all may be predicted from the index AT and ablation site.

Although exact correlation between previous ablation areas and subsequent AT circuits has not been systematically studied, it is well known that extensive AF ablation may create the substrate for AT.^{2,3} Initially, there is only 1 anatomic obstacle in the LA—the mitral valve—which can allow perimitral flutter. After isolation of the PVs, more obstacles are created that can produce the substrate for roof-dependent AT rotating around PVs or PV-related AT.^{1–4} After complex fractionated atrial electrogram ablation, further islands of obstacles are created, which may lead to scar-related AT, or patchy ablation may create slow conduction, allowing the circuit to have N/N-1 wavefront collisions. Under these conditions, the probability of



Figure 4 Examples of prediction of behavior of atrial tachycardia (AT) during ablation. **A**: Anatomic macroreentrant atrial tachycardia (AMAT) as an index AT. **a**: The index AT (cycle length [CL] 272 ms) was a perimitral flutter (Supplemental Video 1A) with a gap between the septal wall and mitral annulus (MA), which was targeted for ablation. **b**: Based on this ablation site, the wavefront collision site septal to the right pulmonary veins was the defined as (N) beat vs (N-1) beat with Δt of 40 ms. **c**: The predicted subsequent second AT circuit is shown by the *yellow arrows*, with CL prolongation of 80 ms (2 × 40 ms). The AT (CL 219 ms) circuit was a localized AT around the anterior scar (Supplemental Video 2A), with a small isthmus between the scar and left atrial appendage (LAA) ostium, which was targeted for ablation. **b**: Based on this targeted ablation site, the wavefront collision on the anterior wall was defined as (N) beat vs (N-1) beats with Δt of 23 ms. **c**: The predicted subsequent second AT circuit is shown by the *yellow arrows*, with CL prolongation of 46 ms (2 × 23 ms). The AT converted to this circuit during ablation at this gap, with the CL increased by 50 ms (Supplemental Video 2B). **d**: If we had created a linear ablation between the anterior scar, the AT would have not converted but terminated because the wavefront collision vorter do the wavefront collision on the anterior scar (Supplemental Video 2B). **d**: If we had created a linear ablation between the anterior scar, the AT would have not converted but terminated because the wavefront scar, the AT would have not converted but terminated because the wavefront collision would have not converted but terminated because the wavefront scar (Supplemental Video 2B). **d**: If we had created a linear ablation between the anterior scar, the AT would have not converted but terminated because the wavefront collision would have been between (N-1) and (N-1) beats. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV

| 8 | Total (n = 194) | Macro (n = 127) | Non-macro (n = 44) | Dual-loop (n = 23) |
|--|-----------------|-----------------|--------------------|--------------------|
| Sensitivity for termination | 99.3 | 100.0 | 96.7 | 100.0 |
| Specificity for termination | 84.4 | 75.0 | 92.9 | 90.9 |
| Accuracy to predict termination | 95.5 | 95.5 | 96.7 | 92.3 |
| Accuracy to predict conversion | 97.4 | 100.0 | 92.9 | 100.0 |
| Accuracy to predict termination/ conversion | 95.9 | 96.1 | 95.5 | 95.7 |

Values are given as percent.

Table 2 Accuracy of the algorithm

AT conversion rather than termination on ablation may potentially increase even if the ablation site is at the correct critical isthmus for treating the index AT.

Requirement for high-resolution mapping

Entrainment mapping is an established electrophysiological technique to identify the arrhythmia mechanism as well as to define components of the reentrant circuit.¹³ The evolution of 3-dimensional electroanatomic mapping systems has allowed electrophysiologists to identify complex circuits, particularly in the setting of abnormal atrial anatomy, regions of scar, and multiple circuits,⁵ thereby reducing the limitations of entrainment mapping. In addition, higher-resolution 3-dimensional electroanatomic mapping leads to improved prediction of the behavior of the index AT on ablation, second AT circuit, and its CL because identification of the exact relationship between the wavefront collision site and the ablation site with a precise activation map of the index AT is required.

Failures of the algorithm

Although the algorithm works in most cases, there are 3 situations in which it might fail.

1. The second AT uses an unmapped chamber (right atrium) or epicardial structure (eg, ligament of Marshall)

In this case, the second AT circuit may be difficult to predict. As mentioned earlier, to predict the behavior of the index AT during ablation, identification of the exact relationship between the wavefront collision site and the ablation site with a precise activation map is required. Figure 5 and Supplemental Video 3 show 2 cases of peritricuspid AT in which the other chamber (LA) was coincidentally mapped and the behavior during ablation was successfully predicted. This example also explains possible prediction failure. To avoid this pitfall, systematic mapping of both chambers and the coronary sinus could be considered, although mapping of epicardial structures such as the vein of Marshall would clearly remain a last resort strategy. However, it would still have the disadvantage of increasing procedure duration while benefitting only a few patients. Alternatively, the operator should map the other chamber or epicardial structures when the result of ablation is contrary to expectations because the AT may jump to or use these structures, which are not mapped at the beginning.

2. Misinterpretation of slow conduction vs complete block (Supplemental Figure 3)

A region thought to represent slow conduction on the activation map may actually be complete block, or the opposite situation may be possible. This misinterpretation may result in index AT behavior during ablation being contrary to prediction because of incorrect assessment of wavefront collision (N-1/N-1 or N-1/N). To avoid this misinterpretation, detailed discrimination of the local electrograms in the region of interest is important even when the high-resolution activation map seems to provide a diagnosis.⁶ Entrainment pacing should be used to confirm the location of the circuit.¹⁴ If the suspected region is at a line of block, tachycardia CL – post-pacing interval measurements should not be close on opposing sides over the line, as one side should be completely out of the circuit.

3. Misinterpretation of AT conversion vs AT slowing of the same circuit (Supplemental Figure 2)

In the present study, of the 148 ATs with termination, 7 (4.7%) became stable with a longer CL during ablation. However, the index ATs did not convert but slowed because of slower conduction and/or subtle change in the ablation

| Table 3 Comparison of CL between the index and subsequer | d subsequent Al |
|--|-----------------|
|--|-----------------|

| | Total | AMAT | Non-AMAT | Multiple-loop AT |
|---|---------------|---------------|---------------|------------------|
| Index AT CL (ms) | 249 (224-298) | 285 (220-350) | 235 (225-288) | 245 (220-283) |
| Predicted CL increase (ms) | 30 (6-48) | 38 (16-54) | 46 (24-61) | 0 (0-0) |
| Observed CL increase (ms) | 35 (8-50) | 40 (18-52) | 40 (25-64) | 3 (0-9) |
| Predicted-observed CL (absolute value) (ms) | 6 (4-9) | 6 (4-9) | 8 (5-11) | 3 (2-6) |
| Subsequent AT CL (ms) | 289 (248-348) | 320 (272–418) | 300 (272–325) | 251 (223–286) |

Values are given as median (25th-75th percentile)

AMAT = anatomic macroreentrant atrial tachycardia; AT = atrial tachycardia; CL = cycle length.

Α

Common flutter jumping to perimitral flutter during ablation on the CTI

В

Common flutter terminated during ablation on the CTI



Figure 5 Algorithm failure (unmapped chamber). Because the opposite side of the chamber is not always mapped when a diagnosis is made from the map in 1 chamber, prediction failure may occur when the circuit uses the chamber or structure that is not mapped from the outset. Both panels show a peritricuspid flutter as the index atrial tachycardia (AT), which is predicted to be terminated. A: We successfully predicted that peritricuspid AT would jump to perimitral AT thanks to the left atrial activation map. Note that the N/N-1 beat collides at the inferior mitral annulus because of slow conduction on the anterior and lateral mitral annulus due to previous ablations (Supplemental Video 3A). B: Conversely, the left atrium (LA) is passively activated from the right atrium, and the wavefront collides at the lateral side of the LA (N/N beat collision) (Supplemental Video 3B). If N/N-1 collision is identified in the chamber or structures that are not mapped during the initial map, an index AT that is predicted to terminate on ablation may convert to a subsequent AT using the other chamber or structures. CTI = cavotricuspid isthmus.

regions. These ATs were actually terminated when the planned linear lesion was completely achieved. To exclude this possibility, entrainment pacing should be performed at several locations on the index AT circuit to determine whether the circuit is still the same.

Clinical implications

We describe a simple mechanism underlying the behavior of AT during ablation and an algorithm that predicts the termination and conversion of ATs upon RF application. The path of subsequent AT circuits may be predicted, which may enable ablation without remapping the entire chamber in combination with entrainment mapping. Knowing this information could help the operator to modify the strategy and to select the most effective ablation line that will take both the active and the possible passive circuit. This could result in a higher termination rate, fewer RF deliveries, and shorter ablation procedures, although this requires further study. Our findings also may lead us to rethink the initial AF procedural strategy, as each ablation region may become a potential obstacle or slow conduction area to cause N/N-1 collision, resulting in potential future iatrogenic ATs.

Study limitations

For analysis of the relationship between the index AT and the second AT, we focused on those that directly converted during ablation, so our findings are not applicable to ATs with a transition having an intervening pause or ectopy or to an induced second AT. Additionally, a few ATs that converted to faster CL did not meet the inclusion criteria in the present study. The mechanism in these ATs should be examined in a further study. Second, although the maximum CL for the passive atrium compatible with conversion vs termination is an interesting issue, lack of systematic mapping in both atria or epicardial structures prevent us from discussing this point. Third, although the prediction accuracy of the algorithm was prospectively studied in the present series, the impact of the ablation strategy using this algorithm requires investigation in a further study. Finally, although the concept should be universally applicable to other mapping systems, the prediction accuracy using other systems has not been confirmed here and requires further investigation.

Conclusion

A simple mechanism underlies the behavior of AT during ablation, even in complex ATs. With a simple algorithm using high-resolution mapping, AT termination/conversion and the subsequent AT circuit and CL can be predicted from the index activation map.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2 018.10.031.

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1746

6. The relationship between wall thickness distribution on CT imaging and substrate mapping on the 3D-EAM in ICM patient

1747

1748 Visualization of potentially arrhythmogenic substrate obtained by cardiac imaging before and during an ablation
 1749 procedure can help focus attention on culprit regions to treat VT.

1750 Late gadolinium-enhanced CMR is the reference technique for tissue characterization and spatial extent, topography, transmurality and heterogeneity of myocardial scar^{102,103}. However, CMR-methods have substantial limitations in 1751 patients with VT in terms of availability, reproducibility across vendors/sites, quality and safety in patients with ICDs. 1752 1753 Moreover, the spatial resolution of conventional CMR-methods (usually several millimeters) may be inadequate to 1754 accurately characterize severely remodeled chronic infarcts. In contrast, MDCT is more readily available, highly 1755 reproducible across vendors/sites, less limited by ICDs, and has unparalleled spatial resolution (about 500µm), and MDCT can accurately assess LV wall thickness (WT)⁸¹. Myocardial wall thinning has been reported to co-localize 1756 with voltage-defined scar as identified using conventional thresholds⁸¹ (peak-to-peak bipolar amplitude <1.5 mV)⁵⁵. 1757 1758 However, the detailed relation between electrophysiological information including near- and far-field voltages, 1759 voltage channels, and VT is thmuses and WT heterogeneity within the scar area has not been thoroughly studied. In 1760 this chapter, we focused on this topic.

- 1761
- 1762

1763 **6-1. Detailed comparison between wall thickness and voltages in chronic myocardial infarction**

1764

1765 Background and purpose

This study aimed to characterize the relation between the regional myocardial WT as imaged by MDCT and EGM amplitudes within scar, including near- and far-field components. We also aimed to clarify which component was automatically considered by the mapping system in different WT regions.

1769 Methods and results

1770 For this study, we enrolled 12 consecutive patients who presented with VT late after myocardial infarction and who 1771 underwent contrast-enhanced MDCT before VT ablation. We performed contrast-enhanced MDCT with a 64-slice 1772 CT scanner (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany) 1 to 3 days before the 1773 ablation procedure. Image processing was performed by 2 trained technicians using the MUSIC software (Liryc-1774 Universite de Bordeaux/INRIA, Sophia Antipolis, France). WT was automatically computed from endo- and 1775 epicardial contours. A 3-dimensional patient-specific model comprising all anatomical information was generated 1776 and exported into 3D-electro anatomical mapping (EAM) systems (Carto 3 system, Biosense Webster) for subsequent 1777 integration with electroanatomical geometries. A voltage map was acquired over the endocardium with a 20-electrode 1778 dedicated catheter (Pentaray, Biosense Webster, Diamond-Bar; multielectrode mapping catheter with 2-6-2 mm 1779 interelectrode spacing and 1mm circumferential electrode) during sinus rhythm (SR) and WT data was merged on 1780 the 3D-EAM and the association between the WT and EGMs were retrospectively analyzd. Although all mapping 1781 points, within the area of WT<5mm, acquired with a 20-electrode dedicated catheter were systematically reviewed,

- bipolar electrograms created from 6mm inter-electrode spacing were removed from the analysis. Signals were filtered
 from 2-240 Hz in unipoles and 16-500 Hz in bipoles, and 50 Hz notch filter was applied.
- 1784

1785 Of 15748 points in total (1312±489 points per patient), 2677 points (within 5mm of the tissue surface) were analyzed.

- 1786 Of these local potentials, 1768 (66.0%) had single-component EGMs, while 909 (34.0%) had multi-component
- 1787 EGMs with LAVAs. The proportion of EGMs with LAVA potentials stratified by the WT was 93/146 (63.7%),
- 1788 214/293 (73.0%), 342/606 (56.4%), 136/441 (30.8%), 98/386 (25.4%) and 26/805 (3.2%), in 0-1mm area, 1-2mm
- area, 2-3mm area, 3-4mm area, 4-5mm area, and \geq 5mm area, respectively (p<0.0001). 785 (86.4%) and 883 (97.1%)
- 1790 LAVAs were distributed in the WT<4mm and the WT<5mm, respectively. In total, approximately 90% of LAVAs
- 1791 were distributed in the WT<4 mm area, and the critical isthmus of the VT was located on the WT 1-4 mm.
- 1792 Although a significant voltage difference was demonstrated in any two of WT ranges in unipolar, bipolar, and far-
- 1793 field EGMs as shown in **Table 6-1**, the general correlation between the voltage and each WT was higher in the far-
- field voltages (unipolar voltage, $\rho=0.348$, p<0.001; bipolar voltage, $\rho=0.380$, p<0.001; far-field voltage, $\rho=0.430$,
- 1795 p<0.001), but still not very strong. In the near-field voltage in multi-component EGMs in the scar area, a significant
- 1796 voltage difference was not seen between any two of them (**Table 6-1**). The correlation was much weaker between the
- 1797 near-field voltage and WT (ρ =0.062, p=0.04).
- 1798

1799 Table 6-1. Comparison of voltages between wall thickness

| Unipolar voltage | WT 0-1mm (N=93) 2.81mV [1.96-4.89mV] | WT 1-2mm (N=250) 3.41mV [2.47-4.49mV] | WT 2-3mm (N=584) 3.58mV [2.82-4.76mV] | WT 3-4mm (N=432) 4.76mV [3.39-6.90mV] | WT 4-5mm (N=382) 5.60mV [3.90-7.26mV] |
|--|---|--|--|--|--|
| WT 0-1mm (N=93) 2.81mV [1.96-4.89mV] | | p=0.981 | p=0.001 | p<0.001 | p<0.001 |
| WT 1-2mm (N=250) 3.41mV [2.47-4.49mV] | | | p<0.001 | p<0.001 | p<0.001 |
| WT 2-3mm (N=584) 3.58mV [2.82-4.76mV] | | | | p<0.001 | p<0.001 |
| WT 3-4mm (N=432) 4.76mV [3.39-6.90mV] | | | | | p<0.001 |
| WT 4-5mm (N=382) 5.60mV [3.9-7.26mV] | | | | | |

| Bipolar voltage | WT 0-1mm (N=146) 0.27mV [0.12-0.45mV] | WT 1-2mm (N=293) 0.36mV [0.19-0.70mV] | WT 2-3mm (N=605) 0.52mV [0.27-0.88mV] | WT 3-4mm (N=441) 1.12mV [0.47-2.04mV] | WT 4-5mm (N=386) 1.18mV [0.61-2.24mV] |
|--|--|--|--|--|--|
| WT 0-1mm (N=146) 0.27mV [0.12-0.45mV] | | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| WT 1-2mm (N=293) 0.36mV [0.19-0.70mV] | | | p<0.001 | p<0.001 | p<0.001 |
| WT 2-3mm (N=605) 0.52mV [0.27-0.88mV] | | | | p<0.001 | p<0.001 |
| WT 3-4mm (N=441) 1.12mV [0.47-2.04mV] | | | | | p=0.007 |
| WT 4-5mm (N=386) 1.18mV [0.61-2.24mV] | | | | | |

| Near-field (LAVA) bipolar voltage | WT 0-1mm (N=93) 0.27mV [0.11-0.44mV] | WT 1-2mm (N=214) 0.28mV [0.14-0.45mV] | WT 2-3mm (N=342) 0.26mV [0.14-0.45mV] | WT 3-4mm (N=136) 0.29mV [0.17-0.49mV] | WT 4-5mm (N=98) 0.29mV [0.17-0.53mV] |
|--|---|--|--|--|---|
| WT 0-1mm (N=93) 0.27mV [0.11-0.44mV] | | p=1.000 | p=1.000 | p=0.995 | p=0.503 |
| WT 1-2mm (N=214) 0.28mV [0.14-0.45mV] | | | p=1.000 | p=1.000 | p=0.571 |
| WT 2-3mm (N=342) 0.26mV [0.14-0.45mV] | | | | p=0.969 | p=0.303 |
| WT 3-4mm (N=136) 0.29mV [0.17-0.49mV] | | | | | p=0.95 |
| WT 4-5mm (N=98) 0.29mV [0.17-0.53mV] | | | | | |

| Far-field bipolar voltage | WT 0-1mm (N=93) 0.14mV [0.08-0.28mV] | WT 1-2mm (N=217) 0.18mV [0.08-0.39mV] | WT 2-3mm (N=342) 0.34mV [0.10-0.65mV] | WT 3-4mm (N=136) 0.56mV [0.22-1.21mV] | WT4-5mm (N=98) 0.70mV [0.43-2.62mV] |
|--|---|--|--|--|--|
| WT 0-1mm (N=93) 0.14mV [0.08-0.28mV] | | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| WT 1-2mm (N=217) 0.18mV [0.08-0.39mV] | | | p<0.001 | p<0.001 | p<0.001 |
| WT 2-3mm (N=342) 0.34mV [0.10-0.65mV] | | | | p<0.001 | p<0.001 |
| WT 3-4mm (N=136) 0.56mV [0.22-1.21mV] | | | | | p=0.001 |
| WT4-5mm (N=98) 0.70mV [0.43-2.62mV] | | | | | |

1806

As shown in **Figure 6-1**, peak-to-peak voltage automatically measured by the 3D-EAM system was composed of only far-field EGM, only near-field EGM, or a combination of the far- and near- field EGMs. The proportion of points from which the system automatically measured voltage on near-field EGM components increased from <10% in areas of wall thickness 4-5mm to 50% in areas <2mm.



Figure 6-1. The relationship between wall thinning and the signal voltages automatically calculated by 3D
 mapping system as a local voltage

| 1810 | |
|------|--|
| 1811 | Summary and conclusions |
| 1812 | The main findings of this study are that |
| 1813 | (1) Far-field voltages may be moderately correlated to the WT. |
| 1814 | (2) Near-field voltages are much less sensitive to the difference in WT. |
| 1815 | (3) The voltage automatically measured by the 3D-EAM is based on near-field EGMs only in the thinnest areas, and |
| 1816 | it is largely based on far-field EGMs in thicker areas. |
| 1817 | (4) Approximately 90% of LAVAs were distributed in the WT<4 mm area, and the critical isthmus of the VT was |
| 1818 | located on the WT 1-4 mm |
| 1819 | In conclusion, we demonstrated that in patients with chronic healed myocardial infarction referred for VT ablation, |
| 1820 | far-filed voltages within the scar show moderate positive correlation with the wall thickness heterogeneity assessed |
| 1821 | by MDCT, but the near-field voltages do not. The automated annotation of bipolar EGMs is more often based on |
| 1822 | near-field EGMs the thinnest areas, in the center of the scar. However, most of the EGMs annotated automatically by |
| 1823 | the 3D-mapping system are far-field, particularly in the wall thickness of 2-5mm scar areas. Most LAVAs are |
| 1824 | distributed in the WT<4mm and the critical site of VT may be distributed in WT:1-4mm area. |
| 1825 | |
| 1826 | |
| 1827 | Manuscript is in publication; J Cardiovasc Electrophysiol. 2019 Feb;30(2):195-204. doi: 10.1111/jce.13767. Epub |
| 1828 | 2018 Oct 31. |
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ORIGINAL ARTICLE

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Detailed comparison between the wall thickness and voltages in chronic myocardial infarction

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Abstract

Background: The relationship between the local electrograms (EGMs) and wall thickness (WT) heterogeneity within infarct scars has not been thoroughly described. The relationship between WT and voltages and substrates for ventricular tachycardia (VT) was examined.

Methods: In 12 consecutive patients with myocardial infarction and VT, WT, defined by a multidetector computed tomography, and voltage were compared. In multicomponent EGMs, amplitudes of both far- and near-field components were manually measured, and the performance of the three-dimensional-mapping system automatic voltage measurement was assessed.

Results: Of 15 748 points acquired, 2677 points within 5 mm of the endocardial surface were analyzed. In total, 909 (34.0%) multicomponent EGMs were identified; 785 (86.4%) and 883 (97.1%) were distributed in the WT less than 4 and 5 mm, respectively. Far-field EGM voltages increased linearly from 0.14 mV (0.08-0.28 mV) in the WT: 0 to 1 mm to 0.70 mV (0.43-2.62 mV) in the WT: 4 to 5 mm (ρ = 0.430; P < 0.001), and a significant difference was demonstrated between any two WT-groups ($P \le 0.001$). In contrast, near-field EGM voltages varied from 0.27 mV (0.11-0.44 mV) in the WT: 0 to 1 mm to 0.29 mV (0.17-0.53 mV) in the WT: 4 to 5 mm with a poorer correlation (ρ = 0.062, P = 0.04). The proportion of points where the system automatically measured the voltage on near-field EGMs increased from less than 10% in areas of WT: 4 to 5 mm to 50% in areas less than 2 mm. Of 21 VTs observed, seven hemodynamically stable VTs were mapped and terminated in WT: 1 to 4 mm area.

Conclusions: Although far-field voltages gradually increase with the WT, near-field does not. The three-dimensional-mapping system preferentially annotates the near-field components in thinner areas (center of the scar) and the far-field

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component in thicker areas when building a voltage map. Critical sites of VT are distributed in WT: 1 to 4 mm areas.

KEYWORDS

computed tomography, ventricular tachycardia, voltage, wall thickness, wall thinning

1 | INTRODUCTION

Visualization of a potentially arrhythmogenic substrate obtained by cardiac imaging before and during an ablation procedure can help focus mapping and ablation on culprit regions to treat ventricular tachycardia (VT). Delayed-enhancement magnetic resonance imaging (MRI) may characterize the spatial extent of myocardial scar, including its topography and transmurality.^{1,2} However, the presence of an implanted cardioverter defibrillator (ICD) may degrade the image quality, and the spatial resolution of MRI (1-2 mm) may be insufficient to accurately characterize scar heterogeneity in thinned myocardial infarction (MI) (down to 1 mm wall thickness [WT]). Contrast-enhanced multidetector computed tomography (MDCT) is shown to assess not only myocardial and vascular anatomy, but also myocardial WT with submillimetric resolution.^{3,4} Myocardial wall thinning has been reported to colocalize with the voltage-defined scar as identified using conventional thresholds,⁵ (peak-to-peak bipolar amplitude <1.5 mV).⁶ However, the detailed relation between local voltages and WT heterogeneity within the scar area has not been thoroughly studied. This study aimed to characterize the relation between the regional myocardial WT as imaged by MDCT and electrogram (EGM) amplitudes within the scar, including near- and far-field components. We also aimed to clarify which component was automatically considered by the mapping system in different WT regions.

2 | METHODS

2.1 | Patient selection

We enrolled 12 consecutive patients who presented with VT late after MI and who underwent contrast-enhanced MDCT before VT ablation. Patients were included if they had episodes of repetitive, sustained VT requiring external cardioversion or ICD interventions. All patients gave written informed consent according to the institutional guidelines of the University of Bordeaux Health System, which provided ethical approval for the study.

2.2 | Image acquisition

We performed contrast-enhanced MDCT with a 64-slice CT scanner (SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany) 1 to 3 days before the ablation procedure as previously reported.⁷ In brief, images were acquired during an expiratory breath-hold with tube current modulation set on end-diastole. CT angiographic images were acquired during a bolus injection of 120 mL of iodinated contrast agent at a rate of 5 mL/s. Acquisition parameters were: slice thickness, 0.6 mm; tube voltage, 120 kVp; maximum tube current, 850 mAs; and gantry rotation time, 330 milliseconds.

2.3 | Image segmentation

Image processing was performed by two trained technicians using the MUSIC software (Liryc-Université de Bordeaux/INRIA, Sophia Antipolis, France). Segmentation was performed as described previously.⁷⁻⁹ In brief, the cardiac chambers, ventricular epicardium, ascending aorta, and coronary sinus (CS) were segmented using semiautomatic methods.⁸ Additional segmentation was performed to identify the coronary arteries and left phrenic nerve.9 WT was automatically computed from endocardial and epicardial contours. A three-dimensional (3D) patient-specific model comprising all anatomical information was generated and exported into a 3D-electroanatomical mapping (EAM) systems (Carto 3 System; Biosense Webster, Diamond Bar, CA) for subsequent integration with electroanatomical geometries. We used a 5-mm value as a cutoff for significant myocardial thinning based on the previous report.¹⁰ End-diastolic WT was displayed as isosurfaces of <1, <2, <3, <4, and <5 mm, respectively (Figure 1A) and displayed on both the endocardial and epicardial surfaces.

2.4 | Electrophysiological study

A 6-Fr decapolar catheter was placed in the CS. The left ventricular (LV) endocardium was accessed by transseptal or retrograde transaortic approach. Pericardial access was obtained via a percutaneous subxiphoid puncture if required.¹¹ A voltage map was acquired over the endocardium with a 20-electrode dedicated catheter (Pentaray; Biosense Webster) multielectrode mapping catheter with 2-6-2-mm interelectrode spacing, and 1-mm circumferential electrode) during sinus rhythm (SR). Signals were filtered from 2 to 240 Hz in unipoles and 16 to 500 Hz in bipoles, and 50-Hz notch filter was applied.

2.5 | Radiofrequency ablation

VT inducibility was assessed with two drive trains (600 and 400 milliseconds) with up to three extra stimuli decremented to 200 milliseconds from the right ventricle (RV) apex. In patients with inducible and tolerated VT, a VT map was acquired and ablation was performed based on the conventional activation map and entrainment





FIGURE 1 Segmented CT image and wall thickness distribution (A) and the registration of the CT-image on the 3D-mapping system in one case (B). (a) Local EGMs in the WT: 2 to 3 mm region show fused EGMs of NF- and FF-components. The NF-voltage (0.52 mV) is larger than FF-voltage (0.21 mV), which is reflected in the peak-to-peak voltage on this site. (b) Local EGMs in the WT: 3 to 4 mm region show separated EGMs of FF- and NF-components. The FF-voltage (1.55 mV) is larger than the NF-voltage (0.41 mV), which is reflected in the peak-to-peak voltage on this site. (b) Local EGMs in the WT: 3 to 4 mm region show separated EGMs of FF- and NF-components. The FF-voltage (1.55 mV) is larger than the NF-voltage (0.41 mV), which is reflected in the peak-to-peak voltage on this site. Blue tags represent LAVAs, mainly distributed in the channel of WT: 2 to 4 mm area surrounded by the border of WT < 2 mm. Ao, aorta; CS, coronary sinus; CT, computed tomography; EGM, electrograms; FF, far-field; LA, left atrium; LAD, left anterior descending artery; LAO, left anterior oblique; LCX, left circumflex artery; LV, left ventricle; NF, near-field EGM; PPV; peak-to-peak voltage; RA, right atrium; RCA, right coronary artery; RV, right ventricle; SVC, superior vena cava; 3D, three-dimensional; WT, wall thickness [Color figure can be viewed at wileyonlinelibrary.com]

mapping. After restoration of SR, or in cases with noninducible VT or VT that was not tolerated, ablation of local abnormal ventricular activities (LAVAs) was performed with the endpoint of LAVA elimination during SR.¹² Ablation was performed using the 3.5-mm open-irrigated catheter and the radiofrequency power was limited to 35 to 50 W endocardially and 25 to 35 W epicardially. After ablation,

the areas previously displaying LAVA were remapped. In the presence of residual LAVAs, further radiofrequency ablation was performed. Induction of VT postablation was repeated with programmed stimulation using the same protocol as before ablation. The procedural endpoint was the complete elimination of LAVAs and noninducibility of VT.
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2.6 | Postprocedural data analysis

2.6.1 | 3D registration

For the postablation analysis, a 3D patient-specific model with all anatomical information was exported into 3D-EAM systems (Carto 3 System; Biosense Webster) for subsequent integration with electroanatomical geometries. WT shells were registered to the electroanatomical map with an operator blinded to the procedure outcome. For 3D registration of EAM geometry with the MDCT model, identifiable anatomic reference points (left atrium, CS, aortic root, LV apex, and mitral annulus) were used as landmarks for alignment and orientation of the 3D-EAM and MDCT models (Figure 1B).

2.6.2 | Comparison between EGMs versus WT

All endocardial SR maps were analyzed. Although all mapping points within the area of WT less than 5 mm acquired with a 20-electrode dedicated catheter were systematically reviewed, bipolar EGM created from 6-mm interelectrode spacing were removed from the analysis. We used an internal point filter software available on the mapping system to limit data acquisition to within 5 mm from the endocardial surface geometry. WT value at each site was compared with both unipolar and bipolar EGM amplitude as automatically measured by the mapping system. Sites exhibiting multicomponent EGMs were assessed by two independent physicians blinded to the CT-imaging information, with adjudication by a third physician in case of disagreement, to determine the presence or absence of LAVAs. As previously reported,¹² LAVAs were defined as sharp high-frequency ventricular potentials, possibly (but not always) of low amplitude, distinct from the far-field ventricular EGM in SR or before the far-field ventricular EGM during VT. To confirm the nature of LAVAs and to distinguish them from far-field ventricular EGMs in the presence of ambiguity, the reaction in pacing maneuvers or local ectopies was used to discriminate near-field

potentials from the far-field.¹² In these areas, both near-field potentials (=LAVAs) and far-field potentials were separately measured and compared with WT, respectively (Figure 1B).

2.7 | Statistical analysis

Categorical data were expressed as numbers and percentages. Continuous data were expressed as mean ± SD and/or median (25th-75th percentiles) according to the skewness. Comparison between each voltage (unipolar, bipolar, near-field, and far-field) and the stratum of WT was performed with the nonparametric Kruskal-Wallis test and the Dunnett T3 post-hoc test. The general correlation between the voltage and WT was assessed with the Pearson correlation test. To test confidence in LAVA potentials' determination, the interobserver agreement was evaluated by calculating the Cohen's κ coefficient. Far- and near-field EGMs in WT more than 5 mm was not included in the analysis because of an extremely small distribution of LAVAs in this region, which could incorrectly affect the statistics. *P* < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The baseline characteristics of the 12 patients are shown in Table 1. MI were observed in inferior wall in seven (58.3%), the anterior wall in six (50.0%), and lateral in two (14.3%) patients. Of 15 748 points in total (1312 ± 489 points per patient), 2677 points (within 5 mm of the tissue surface) were analyzed. Of these local potentials, 1768 (66.0%) had single component EGMs, while 909 (34.0%) had multicomponent EGMs with LAVAs. The proportion of EGMs with LAVA potentials stratified by the WT was 93 of 146 (63.7%), 214 of 293 (73.0%), 342 of 606 (56.4%), 136 of 441 (30.8%), 98 of 386

| Patient no. | Age | Sex | Procedure no. | NYHA | Amiodarone | β-Blocker | LVEF | ICD | Infarct region |
|-------------|-----|-----|---------------|------|------------|-----------|------|-----|----------------------------|
| 1 | 76 | М | 1 | 3 | n | Y | 35 | У | Anterior |
| 2 | 80 | М | 1 | 1 | У | Υ | 23 | у | Anteroseptal, apical |
| 3 | 51 | М | 1 | 1 | n | Y | 35 | У | Anterior |
| 4 | 72 | М | 1 | 2 | У | Υ | 42 | у | Inferolateral |
| 5 | 26 | М | 2 | 1 | n | Y | 29 | У | Anterior |
| 6 | 78 | М | 1 | 4 | У | Υ | 35 | у | Anterior |
| 7 | 71 | М | 1 | 1 | У | Y | 35 | у | Anteroseptal, inferoseptal |
| 8 | 56 | М | 1 | 2 | У | Υ | 40 | у | Inferior |
| 9 | 71 | М | 1 | 1 | У | Y | 50 | У | Inferior |
| 10 | 70 | М | 1 | 2 | У | Υ | 40 | у | Inferior |
| 11 | 55 | М | 1 | 2 | У | Y | 30 | У | Inferior, lateral |
| 12 | 64 | М | 1 | 1 | n | Y | 65 | y | Inferior |

TABLE 1 Baseline characteristics

Abbreviations: ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

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| TABLE 2 | Comparison of voltages between wall thickness. | A. Unipolar voltages. B. Bipola | r voltages. C. Near-field (LAVA) | voltages. D. Far-field |
|----------|--|---------------------------------|----------------------------------|------------------------|
| voltages | | | | |

| | WT 0-1 mm (N = 93) 2.81 mV | WT 1-2 mm (N = 293) 3.41 mV | WT 2-3 mm (N = 605) 3.58 mV | WT 3-4 mm (N = 441) 4.76 mV | WT 4-5 mm (N = 386) 5.60 mV |
|---|--|---|---|---|--|
| Unipolar voltage | [1.96-4.89 mV] | [2.47-4.49 mV] | [2.82-4.76 mV] | [3.39-6.90 mV] | [3.90-7.26 mV] |
| WT 0-1 mm (N = 93) 2.81 mV [1.96-4.89 mV] | | <i>P</i> = 0.981 | <i>P</i> = 0.001 | P < 0.001 | P < 0.001 |
| WT 1-2 mm (N = 293) 3.41 mV [2.47-4.49 mV] | | | P < 0.001 | P < 0.001 | P < 0.001 |
| WT 2-3 mm (N = 605) 3.58 mV [2.82-4.76 mV] | | | | P < 0.001 | P < 0.001 |
| WT 3-4 mm (N = 441) 4.76 mV [3.39-6.90 mV] | | | | | P < 0.001 |
| WT 4-5 mm (N = 386) 5.60 mV [3.9-7.26 mV] | | | | | |
| | WT 0-1 mm (N = 146) 0 27 mV | WT 1-2 mm (N = 293) 0.36 mV [0 19-0 70 | WT 2-3 mm (N = 605) 0.52 mV [0 27-0 88 | WT 3-4 mm (N = 441) 1.12 mV [0 47-2 04 | WT 4-5 mm (N = 386) 1.18 mV [0.61-2 24 |
| Bipolar voltage | [0.12-0.45 mV] | mVl | mVl | mVl | mVl |
| WT 0-1 mm (N = 146) 0.27 mV [0.12-0.45 mV] | | P < 0.001 | P < 0.001 | P < 0.001 | P < 0.001 |
| WT 1-2 mm (N = 293) 0.36 mV [0.19-0.70 mV] | | | P < 0.001 | P < 0.001 | P < 0.001 |
| WT 2-3 mm (N = 605) 0.52 mV [0.27-0.88 mV] | | | | P < 0.001 | P < 0.001 |
| WT 3-4 mm (N = 441) 1.12 mV [0.47-2.04 mV] | | | | | <i>P</i> = 0.007 |
| WT 4-5 mm (N = 386) 1.18 mV [0.61-2.24 mV] | | | | | |
| Near-field (LAVA) | WT 0-1 mm (N = 93) | WT 1-2 mm (N = 214) | WT 2-3 mm (N = 342) | WT 3-4 mm (N = 136) | WT 4-5 mm (N = 98) |
| bipolar | 0.27 mV | 0.28 mV | 0.26 mV | 0.29 mV | 0.29 mV |
| voltage $WT = 0.1 \text{ mm} (N = 0.3)$ | [0.11-0.44 mV] | [0.14-0.45 mV] | [0.14-0.45 mV] | [0.17-0.49 mV] | [0.17-0.53 mV] |
| 0.27 mV [0.11-0.44 mV] | | P - 1.000 | P = 1.000 | P = 0.775 | P = 0.303 |
| WT 1-2 mm (N = 214) 0.28 mV [0.14-0.45 mV] | | | <i>P</i> = 1.000 | <i>P</i> = 1.000 | P = 0.571 |
| WT 2-3 mm (N = 342) 0.26 mV [0.14-0.45 mV] | | | | P = 0.969 | P = 0.303 |
| WT 3-4 mm (N = 136) 0.29 mV [0.17-0.49 mV] | | | | | P = 0.95 |
| WT 4-5 mm (N = 98) 0.29 mV [0.17-0.53 mV] | | | | | |
| Far-field voltage bipolar voltage | WT 0-1 mm (N = 93) 0.14 mV [0.08-0.28 mV] | WT 1-2 mm (N = 217) 0.18 mV [0.08-0.39 mV] | WT 2-3 mm (N = 342) 0.34 mV [0.10-0.65 mV] | WT 3-4 mm (N = 136) 0.56 mV [0.22-1.21 mV] | WT4-5mm (N = 98) 0.70 mV [0.43-2.62 mV] |
| WT 0-1 mm (N = 93) | | P < 0.001 | P < 0.001 | P < 0.001 | P < 0.001 |
| 0.14 mV [0.08-0.28 mV] | | | | | |
| WT 1-2 mm (N = 217) 0.18 mV [0.08-0.39 mV] | | | P < 0.001 | P < 0.001 | P < 0.001 |
| WT 2-3 mm (N = 342) 0.34 mV [0.10-0.65 mV] | | | | P < 0.001 | P < 0.001 |
| WT 3-4 mm (N = 136) 0.56 mV [0.22-1.21 mV] | | | | | <i>P</i> = 0.001 |
| WT4-5mm (N = 98) 0.70 mV [0.43-2.62 mV] | | | | | |

Abbreviation: WT, wall thickness.

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(25.4%), and 26 of 805 (3.2%), in 0 to 1-mm area, 1 to 2-mm area, 2 to 3-mm area, 3 to 4-mm area, 4 to 5-mm area, and more than 5 mm area, respectively (P < 0.0001). Hence, 785 (86.4%) and 883 (97.1%) LAVAs were distributed in the WT less than 4 mm and the WT less than 5 mm, respectively. The Cohen's κ coefficient for intraobserver and interobserver agreement with LAVAs was 0.92 (95% confidence intervals [CI], 0.90-0.94) and 0.87 (95% CI, 0.84-0.90), respectively.

3.2 | Voltage vs WT

In addition to the median amplitude of unipolar and bipolar EGMs as automatically measured by the 3D-EAM system, we investigated the amplitude of bipolar near- and far-field amplitudes stratified by the WT. Unipolar voltage increased from 2.81 mV [1.96-4.89 mV] to 5.60 mV [3.90-7.26 mV] and bipolar voltage increased from 0.27 mV (0.12-0.45 mV) to 1.18 mV (0.61-2.24 mV) as WT increased from 0 to 1 mm to 4 to 5 mm, and significant differences were detected in the comparison between any two of the WT except WT 0 to 1 mm vs 1 to 2 mm in the unipolar (Table 2A and 2B). The far-field voltage amplitude in multicomponent EGMs in the scar area was varying from $0.14 \,\text{mV}$ (0.08-0.28 mV) to $0.70 \,\text{mV}$ (0.43-2.62 mV) as WT increased from 0 to 1 mm to 4 to 5 mm. Similarly, a significant voltage difference was demonstrated in any two of them (Table 2C). Although a significant voltage difference was demonstrated in any two of WT ranges in unipolar, bipolar, and far-field EGMs, the general correlation between the voltage and each WT was higher in the farfield voltages (unipolar voltage, ρ = 0.348, P < 0.001; bipolar voltage, ρ = 0.380, P < 0.001; far-field voltage, ρ = 0.430, P < 0.001) but still not very strong.

In the near-field voltage in multicomponent EGMs in the scar area, a significant voltage difference was not seen between any two of them (Table 2D). The correlation was much weaker between the near-field voltage and WT ($\rho = 0.062$, P = 0.04). For the assessment of the voltage correlation between 0 to 1 mm to 4 to 5 mm, no individual patient significantly skewed the data as the mean number of measurements by the patient was similar between each stratum of WT (P = 0.85).

3.3 | Automated peak-to-peak voltage measurements

As shown in Figure 2A, peak-to-peak voltage automatically measured by the 3D-EAM system was composed of only far-field EGM, only near-field EGM, or a combination of the far- and near-field EGMs. The proportion of points from which the system automatically measured voltage on near-field EGM components increased from less than 10% in areas of WT 4 to 5 mm to 50% in the areas less than 2 mm.

In scar areas with LAVAs, 2% of EGMs' amplitude exceeded 1.5 mV in the WT 0 to 1 mm area as compared with 40% in the WT 4 to 5 mm. At sites with normal voltage (\geq 1.5 mV), the mapping system automatically selected the near-field component, 100% in the WT 0 to 1 mm versus 0% in the WT 4 to 5 mm (Figures 2B and 3).

Altogether, only a few points with normal voltage (>1.5 mV) were measured from near-field EGMs, and most were measured from the far-field EGMs in the scar. Most of the LAVA near-field EGMs were less than 0.5 mV (701 of 909; 77.1%), and (893 of 909; 98.2%) of those were less than 1.5 mV in the scar area.

3.4 | Radiofrequency ablation

Radiofrequency ablation targeting LAVA was performed endocardially first in all patients. Monomorphic VT was induced mechanically or by programmed pacing in all patients. In total, 21 VTs (induced or spontaneous) were observed, and seven hemodynamically stable VTs were mapped in six patients using conventional and entrainment mapping. All were successfully terminated with endocardial ablation: over an area of 1 to 2 mm thickness in two VTs, 2 to 3 mm in three, and 3 to 4 mm in two (Figure 3B). After termination of VT in these cases, further ablation targeting LAVAs was performed during SR. Complete elimination of LAVAs was not achieved despite extensive ablation in four patients and one patient could not tolerate a long procedure. Although clinical VT was not inducible in any patients by the same pacing protocol as before ablation, nonclinical VT was induced in four patients including two with polymorphic VT; two with complete LAVA elimination; and two with partial LAVA elimination. Additional RF applications were performed for patients with nonclinical VT based on the pace-map without further induction. The mean procedure time and ablation times were 269±45 and 49 ± 15 minutes, respectively. During a follow-up of 21.1 ± 16.4 months, recurrent VT was revealed on ICD interrogation in three patients: complete LAVA elimination had not been achieved in two. and nonclinical VT had been induced at the end of the previous procedure in 1.

4 | DISCUSSION

In this study, we analyze the relation between voltage and myocardial WT heterogeneity within chronic MI. The main findings are that (1) far-field voltages may be moderately correlated to the WT; (2) near-field voltages are much less sensitive to the difference in WT; (3) the voltage automatically measured by the 3D-EAM is based on near-field EGMs only in the thinnest areas, and it is largely based on far-field EGMs in thicker areas; (4) approximately 90% of LAVAs were distributed in the WT less than 4 mm area, and the critical isthmus of the VT was located on the WT 1 to 4 mm.

4.1 | Relationship between WT and voltage

Our results are consistent with prior studies, which indicate a positive correlation between unipolar and bipolar voltage and WT within chronic MI. In addition, the current study provided a further characterization of the relation between WT using CT scan, voltages and the nature of the EGMs recorded. A prior endocardial and epicardial mapping study reported transmural electrophysiological

substrate in thinnest myocardial areas.^{1,2,13} Furthermore, some studies with late gadolinium-enhanced MRI showed that endocardial unipolar and bipolar EGM amplitudes decreased significantly with increasing scar transmurality on MRI.^{2,14}

From the finding in the current study, far-field voltages showed a stronger correlation with the WT in the scar area, and automated bipolar/unipolar voltages provided less correlation probably because the peak-to-peak voltage automatically measured with the 3D-EAM might be contributed by both near- and far-filed EGMs. We clearly demonstrated that in the bipolar EGMs where far- and near-field signals could be separately identified, many of these voltages were measured on near-field EGMs in thinner WT (<2 mm) and on far-field ones when WT exceeded 2 mm. This difference could be due to the absence of a far-field signal coming from the third dimension (WT) in the thinnest scar. The total far-field effect may depend on the local WT and adjacent healthy tissues, which may finally affect the bipolar voltage. This annotation issue is an important limitation of automated mapping systems and should be acknowledged in the interpretation of both voltage and activation maps. This can explain why approximately 20% of EGMs are reported to show normal voltages even in the transmural scar on MRI, and critical VT ablation sites in some patients are located within these areas.² Although the direct comparison between the transmurality of the MRI-defined scar and the WT of the CT-defined scar is not easy, normal voltage EGMs in a MRI-defined transmural scar in the previous study may be mostly due to far-field EGMs, possibly masking/missing the smaller nearfield EGMs. This finding also supports the suboptimal results of voltage-channel based ablation strategy¹⁵ (Figure 3A). As shown in the current study, unipolar, bipolar, and far- and near-field amplitudes did not demonstrate a strong correlation to the WT, which underscored that voltage and CT-based WT may have a moderate correlation but provide more or less different information and should be used complimentarily.

4.2 | Discrepancy between near- and far-field EGM components

Interestingly, we found near-field bipolar voltage much less closely related to thickness heterogeneity than far-field bipolar voltage. As we mentioned, the relation between far-field bipolar voltage and thickness may be explained by the fact that the far-field EGM emerges from a larger area that includes more remote myocardium,¹⁶ and the amount of such remote myocardium is likely to decrease when the wall gets thinner and mostly composed of the scar.

In contrast, the near-field EGM emerges from bundles of surviving myocardium within the scar located between the pairs of bipolar.¹⁶ These EGM components characterize a more microscopic structural feature, and the amount of such tissue does not seem to relate to the thickness of the entire wall. In addition, closely spaced bipoles may only detect superficial LAVAs, missing those that are deeper in the scar, fibrosis possibly acting as an insulator for recording these deeper activities. Finally, these tiny EGMs may be

masked by the far-field from thicker adjacent regions hosting many more "healthy" myocytes.

As for the substrate ablation, LAVAs represented by near-field EGMs in the scar may be targeted. WT can help to predict where these surviving fibers are; approximately 90% of them are distributed in the WT less than 4 mm area and more than 95% are in the WT less than 5 mm area. However, approximately 80% of the LAVA amplitudes are less than 0.5 mV, which does not vary much and has no strong correlation to the WT. This observation may suggest that the surviving bundles in the scar are made of a fairly consistent amount of cells at a given point.

4.3 | Relationship between WT and VT termination site

The architecture of scar after MI is well known.¹⁷⁻¹⁹ From the endocardium to the epicardium, the wall is composed of scar potentially intermingled with surviving myocardial fibers, overlaid by a layer of remote myocardium whose thickness is decreasing with scar transmurality. The current study shows that LAVAs are more



FIGURE 2 The relationship between wall thinning and the signal voltages automatically calculated by 3D mapping system as a local voltage in general (A) and in the area >1.5 mV (B)



FIGURE 3 Continued.

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likely distributed within thinner areas typically in WT less than 2 mm. However, in the current study, VT terminations during ablation were observed when ablating in areas with the WT: 1 to 4 mm. This finding suggested that some LAVAs identified in the WT 0 to 1 mm and 4 to 5 mm may not be associated with critical sites of VTs. Although the VT substrate was reported to be more often localized within the scar vs in the border zone,^{1,2,20} the thinnest area of WT 0 to 1 mm may not be the critical channel for the VT circuit but rather a zone of the block (functional or not). The WT 1 to 4 mm may include more a combination of fibrosis and surviving myocardium known to be associated with increased anisotropy and slow conduction critical to the VT circuit. One recent study reported a thicker WT as a targeted ablation site.²¹ This discrepancy might be explained by the different ablation strategy in which they targeted border areas closer to the healthy areas (which were probably thicker). We outlined that the importance of high spatial resolution imaging was to characterize the structural substrate of VT in chronic infarcts. These results on WT distribution from MDCT could be used to better map and ablate post-MI VTs.

4.4 | Clinical implications

By analyzing both far- and near-field signals in the scar, the present finding provides further characterization of the relation between WT and voltages. As local near-field activity in the scar area is targeted for ablation, the finding that bipolar voltage reflects more far-field EGMs in the thicker scar area helps the interpretation of voltage/ activation maps. In addition, approximately 90% of VT substrate was distributed in the WT less than 4 mm and the critical sites for VT ablation might be localized in the WT: 1 to 4 mm area. This is an important observation as we know that CT scan underestimates the surface of the scar when compared with MRI but it may show the part of the scar that matters and hosts VT isthmus channels.

4.5 | Study limitations

First, this study included a small sample size without females and the findings might not be extrapolated to the nonischemic VT and female patients. Second, contact force may impact on recorded amplitude but no multipolar mapping catheters are capable of contact force measurement so far. Third, voltage amplitude measurement is related

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to the relationship between the two unipolar electrodes comprising the bipolar EGM, which may be dependent on the catheter orientation. However, this limitation cannot be completely removed in any similar studies, because the activation within heterogenous scar tissue is originally complex and has a zig zag pattern, and these 3D activation patterns might not be displayed perfectly with the two-dimensional mapping catheter. Fourth, the results of this study should be applied to voltages and EGMs morphology recorded by the specific platform of the mapping catheter (Pentaray). Smaller electrode size, unidirectional rather than the circumferential electrode,22 smaller interelectrode spacing^{22,23} may attenuate bipolar far-field effect, leading to a different result. Fifth, LAVA analysis was performed manually and algorithms would be desirable to ensure standardization and reproducibility. Another limitation was related to the potential misregistration between imaging and electroanatomical mapping geometries. This aspect was partly addressed by using state-of-the-art technologies embedded in the 3D-EAM system. Therefore, one should be aware that all reported correlations between imaging and mapping data were subjected to underestimation. The absence of MRI could also be a limitation as the relation between WT and scar transmurality could be viewed as speculative. However, a prior study has shown that WT related to the transmurality of the electrophysiological VT substrate.^{3-5,7,8}

5 | CONCLUSIONS

In patients with chronically healed MI referred for VT ablation, farfield voltages within the scar showed moderate positive correlation with the WT heterogeneity assessed by MDCT, but the near-field voltages do not. The automated annotation of bipolar EGMs was more often based on near-field EGMs of the thinnest areas, in the center of the scar. However, most of the EGMs annotated automatically by the 3D-mapping system are far-field, particularly in the WT of 2 to 5 mm scar area. Approximately 90% of LAVAs are distributed in the WT less than 4 mm and the critical site of VT might be distributed in WT: 1 to 4 mm area.

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FIGURE 3 Comparison between the voltage map and wall thickness map. MDCT demonstrates heterogeneous WT distribution (<5 mm) larger than the low voltage area (<1.5 mV) in both patients; (A) with an inferior scar and (B) in inferior and apical scars. (A) Note that the false-positive normal voltage channel (>1.5 mV, 3-5 mm WT) (white arrows) is displayed in the automated peak-to-peak voltage map as the 3D-EAM system misses LAVAs (=0.22 mV) and takes the largest peak-to-peak amplitude as a local voltage. (B) Note that, in the dense scar area (<0.5 mV, <2 mm WT), voltage is based on delayed near-field EGMs with multiple components (a), while in the normal voltage area (>1.5 mV, 4-5 mm WT), voltage is based on a combination of far- and near-field signal (b). Purple tags show LAVA distribution during SR. During the clinical VT, diastolic potentials (c), were identified on the green tags in the dense scar area <0.5 mV. Interestingly, while there is no channel on the voltage map, one can see it on the CT scan. It appears as a relatively preserved thickness channel clearly visible on 2 to 3 mm WT area bordered by thinner areas (yellow dotted line). CS, coronary sinus; DP, diastolic potential; CT, computed tomography; IVC, inferior vena cava; LA, left atrium; LAVA, local abnormal ventricular activity; LIPV, left ventricular pulmonary vein; MDCT, multidetector computed tomography; RA, right atrium; SR, sinus rhythm; VT, ventricular tachycardia; WT, wall thickness [Color figure can be viewed at wileyonlinelibrary.com]

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1851

6-2. Are wall thickness channels defined by computed tomography predictive of isthmuses of 1852 post-infarction ventricular tachycardia?

1853

1854 Background and purpose of the study

- 1855 We have demonstrated in detail the correlation between the voltages and WT distribution in the prior study. 1856 Additionally, we found that critical ablation site to terminate the VT is localized on the region with the WT of 1-1857 4mm. However, WT maps have not been directly compared to activation maps during VT in the first study (Chapter 1858 **6-2**). We hypothesized that areas of severe thinning are indicative of denser scar acting as zones of conduction block, 1859 and that VT-isthmuses would instead be observed in channels of relatively preserved thickness within scars. This 1860 study aimed to characterize the relationship between WT channels derived from MDCT and VT-isthmuses as defined
- 1861 by high density activation mapping, 'RhythmiaTM'.

1862 Methods and results

- 1863 For this study, an entire VT circuit has to be displayed as a gold standard to be compared with the CT WT distribution.
- 1864 Therefore, of 30 consecutive patients who underwent CA for post-myocardial infarction VT using the OrionTM
- multipolar basket catheter and the RhythmiaTM system (Boston Scientific, Marlborough, MA, USA), 9 patients with 1865
- 1866 complete VT activation maps which covers an entire CL were included. Image acquisition and processing was 1867 performed similarly as it was done in the first study (Chapter 6-2).
- 1868 The 3D-EAM was merged on the MDCT geometries on the RhythmiaTM system using identifiable anatomic reference
- 1869 points (Superior vena cava, inferior vena cava, left atrium, CS, aortic root, LV apex, and the MA [3, 6, 9, and 12
- 1870 o'clock]) to align both surfaces. The analyses were then performed using custom-built software in Matlab (The
- 1871 Mathworks, Inc., Nattick, MA).
- 1872 On MDCT data, a CT-channel was defined according to the following 3 criteria
- 1873 1. Abnormal thickness (<5 mm)
- 1874 2. Thickness on both edges thinner than that inside the channel.
- 1875 3. Length longer than width.
- 1876 CT-channels were identified by a consensus of blinded analyses by 3 trained physicians (one radiologist and two
- 1877 electrophysiologists). The contours of each CT-channel were traced on the CT geometry.
- 1878 On electroanatomical maps, a VT-isthmus was defined as follows.
- 1879 1. Regions sequentially activated during the diastolic phase of VT
- 1880 2. Confirmed by entrainment pacing or direct termination during ablation on the site with the diastolic potentials.
- 1881 Additionally, the VT-isthmus was divided into three portions based on the local activation time in the activation map
- 1882 in the present study; the first third of the diastolic phase is referred to as the entrance (early diastolic phase), the
- 1883 second third as the central isthmus (mid-diastolic phase), and the last third as the exit (late diastolic phase).
- 1884
- 1885 In total, 32 different VTs (median 4 per patient) were observed, of which complete activation maps were acquired in
- 1886 10 (mean CL=429+/-77ms). Of the 10 VTs in which the VT circuit was fully characterized by activation mapping
- 1887 covering an entire CL, all VT-isthmuses co-localized with CT-channels. Two example cases were shown in the Figure
- 1888 6-2.



1890 Figure 6-2. VT activation map merged on the WT-map.

Example (A) shows clinical monomorphic VT in 59yo man with inferolateral infarction. One CT-channel covered diastolic activation as shown in three EGMs, where WT of the CT-channel is 2-4mm, and the edge is <2mm and mitral annulus. VT was terminated during ablation in this location, and the same VT was not induced after ablation at this site. Example (B) shows recurrent monomorphic VT in 71yo man with inferolateral infarction. Complete LAVA elimination with non-inducibility was achieved endocardially at the previous session. CT-channel corresponded with epicardial VT-isthmus where the central WT is 2-4mm bordered between the dense scar<2mm and mitral annulus. Epicardial EGMs on the isthmus are shown in the figure.

1897

- The comparison between CT-channels and VT-isthmuses are described in the **Table 6-2.** Out of the 41 CT-channels identified in the population, 21(51.2%) contained diastolic potentials during VT. These electrical VT-isthmuses went through a single CT-channel in 3(30%) VTs, 2 CT-channels in 2(20%), 3 CT-channels in 3(30.0%), and 4 CT-channels in 2(20.0%). Therefore, channels defined by CT predict involvement in a critical part of the VT circuit with a sensitivity of 100% and a positive predictive value of 51.2%.
- 1903 Electrophysiological VT-isthmuses were more likely to be associated with CT-channels that were longer [P=0.04,
- OR 1.05/mm], thinner (but not less than 1mm) [P=0.03, OR 0.36/mm], or parallel to the mitral annulus [P=0.07,
 OR3.93].
- 1906

| VT No (Total number of CT-channels) | VT-1 (N=4) | VT-2 (N=7) | VT-3 (N=7) | VT-4 (N=7) | VT-5 (N=3) | VT-6 (N=4) | VT-7 (N=7) | VT-8 (N=1) | VT-9 (N=5) | VT-10 (N=3) |
|---|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|
| Isthmus (entrance, center, or exit), n (%) | 2(50.0%) | 4(66.7%) | 4(57.1%) | 3(42.9%) | 1(33.3%) | 2(50.0%) | 3(42.9%) | 1(100%) | 1(20.0%) | 3(100%) |
| Isthmus (entrance), n (%) | 2(50.0%) | 2(28.6%) | 3(42.9%) | 2(28.6%) | 1(33.3%) | 2(50.0%) | 3(42.9%) | 1(100%) | 1(20.0%) | 2(66.7%) |
| Isthmus (central isthmus), n (%) | 1(25.0%) | 1(16.7%) | 3(42.9%) | 2(28.6%) | 1(33.3%) | 1(25.0%) | 3(42.9%) | 1(100%) | 1(20.0%) | 2(66.7%) |
| Isthmus (exit), n (%) | 1(25.0%) | 3(42.9%) | 2(28.6%) | 2(28.6%) | 1(33.3%) | 1(25.0%) | 2(28.6%) | 1(100%) | 1(20.0%) | 2(66.7%) |
| Entire VT-isthmus is covered by CT-channel. v or n | у | У | у | У | У | у | у | у | у | У |

- 1907 Table 6-2. CT-channel vs. VT-isthmus per VT
- 1908

1909 Summary and conclusion

In conclusion, CT scan wall thickness maps identify CT-channels which host VT-isthmuses consistently. Half of the CT-defined channels are associated with the critical isthmus of mapped VT. If not all CT-channels are functional VTisthmuses, perhaps due to VT non-inducibility, longer and thinner (but>1mm) CT-channels parallel to the mitral annulus are more frequently associated with VT-isthmuses. The integration of these 3D models describing clear and focused targets could help to shorten VT ablation procedures, and potentially improve outcomes, but the clinical impact of this approach needs to be tested in further prospective trials.

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Are wall thickness channels defined by computed tomography predictive of isthmuses of postinfarction ventricular tachycardia? <a>©

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BACKGROUND Wall thickness (WT) in post-myocardial infarction scar is heterogenous, with channels of relatively preserved thickness bordered by thinner scar.

OBJECTIVE This study sought to determine whether 3-dimensionallyreconstructed computed tomography (CT) channels correlate with electrophysiological isthmuses during ventricular tachycardia (VT).

METHODS We retrospectively studied 9 postinfarction patients (aged 57 \pm 15 years, 1 female) with 10 complete VT activation maps (cycle length 429 \pm 77ms) created using high-resolution mapping. Three-dimensionally-reconstructed WT maps from CT were merged with the activation map during sinus rhythm (SR) and VT. The relationship between WT and electrophysiological characteristics was analyzed.

RESULTS A total of 41 CT channels were identified (median 4 per patient), of median (range) length 21.2 mm (17.3–36.8 mm), width 9.0 mm (6.7–16.5 mm), and area 1.49 cm²(1.00–1.75 cm²). WT in the channel was significantly thicker in the center than in the edge (median 2.4 mm vs 1.5 mm, P < .0001). Of 3163 (2493–5960) mapping points in SR, 382 (191–1115) local abnormal ventricular activities (LAVAs) were

Introduction

Visualization of potentially arrhythmogenic substrate obtained by cardiac imaging before and during an ablation procedure can help focus attention on culprit regions to treat ventricular tachycardia (VT). identified. One patient had a maximal proportion of LAVAs in 3–4 mm, 3 patients in 2–3 mm, 2 in 1–2 mm, and 2 in 0–1 mm. The VT isthmuses of all 10 VTs corresponded with 1–4 CT channels. Twenty-one of the 41 CT channels (51.2%) corresponded to a VT isthmus (entrance, mid, or exit). Electrophysiological VT isthmuses were more likely to be associated with CT channels that were longer (P = .04, odds ratio [OR] 1.05/mm), thinner (but not less than 1 mm) (P = .03, OR 0.36/mm), or parallel to the mitral annulus (P = .07, OR 3.93).

CONCLUSION VT isthmuses were always found in CT channels (100% sensitivity), and half of CT channels hosted VT isthmuses (positive predictive value 51%). Longer and thinner (but >1 mm) CT channels were significantly associated with VT isthmuses.

KEYWORDS Contrast-enhanced multidetector computed tomography; High-resolution mapping; Isthmus; MUSIC; Myocardial infarction; Ventricular tachycardia; Wall thickness

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Late gadolinium–enhanced cardiac magnetic resonance (CMR) is the reference technique for tissue characterization and spatial extent, topography, transmurality, and heterogeneity of myocardial scar.^{1,2} However, CMR methods have substantial limitations in patients with VT in terms of

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availability, reproducibility across vendors/sites, quality, and safety in patients with implantable cardioverter-defibrillators (ICDs).^{3,4} Moreover, the spatial resolution of conventional CMR methods (usually several millimeters) may be inadequate to accurately characterize severely remodeled chronic infarcts. In contrast, multidetector computed tomography (MDCT) is more readily available, is highly reproducible across vendors/sites, is less limited by ICDs, and has unparalleled spatial resolution (about 500 μ m), and MDCT can accurately assess left ventricular (LV) wall thickness (WT).^{5,6} Wall thinning has been shown to colocalize with voltage-defined scar (peak-to-peak bipolar amplitude <1.5 mV),⁷ but to our knowledge WT maps have not been directly compared to activation maps during VT. We hypothesized that areas of severe thinning are indicative of denser scar acting as zones of conduction block, and that VT isthmuses would instead be observed in channels of relatively preserved thickness within scar. This study aimed to characterize the relationship between WT channels derived from MDCT and VT isthmuses as defined by high-density activation mapping.

Methods Patient selec

Patient selection

Of 30 consecutive patients who underwent catheter ablation for post-myocardial infarction (MI) VT using the Orion multipolar basket catheter and the Rhythmia system (Boston Scientific, Marlborough, MA), 9 patients with complete VT activation maps covering an entire cycle length (CL) were included. All patients had episodes of repetitive, sustained VT requiring external cardioversion or ICD interventions. The research was approved by local ethics committees. Prior written informed consent to participate was obtained from all participants, according to institutional guidelines.

Image acquisition

Contrast-enhanced MDCT was performed with a 2×192 detector dual-source scanner (Somatom Force, Siemens Healthcare, Forchheim, Germany), 1–3 days prior to the ablation procedure. Images were acquired in mid-diastole using prospective electrocardiogram triggering during an expiratory breath-hold, with tube voltage and current adapted to patient morphology. Acquisition was performed in the arterial phase after the injection of a dual-phase bolus of iodinated contrast agent, ie, 60 mL of 100% contrast at the rate of 5 mL/s, followed by 80 mL of 50%/50% contrast/saline at the same rate.

Image segmentation

Image processing was performed by 2 trained technicians using the MUSIC platform (Liryc, Université de Bordeaux, Bordeaux, France, and INRIA, Sophia Antipolis, France), as described previously.^{8–11} Briefly, the cardiac chambers, ventricular epicardium, ascending aorta, and coronary sinus (CS) were segmented semi-automatically,⁹ and ventricular endocardium automatically. WT was automatically computed from endocardial and epicardial contours. We used 5 mm as a cutoff for significant myocardial thinning based on previously reported MDCT values of WT in a healthy population.¹¹ Severely thinned scar areas are defined as WT<2 mm. A 3-dimensional (3D) patient-specific model comprising all anatomical information was generated and exported in MAT-LAB (Mathworks, Inc, Natick, MA) for subsequent post hoc integration with electroanatomical geometries.

Electrophysiological study

Electrophysiological studies were performed blinded from MDCT results. A 5F decapolar and quadripolar catheter were placed in the CS and the right ventricle, respectively. The LV endocardium was accessed using a transseptal approach. Pericardial access was obtained via a percutaneous subxiphoid puncture if required.^{12,13} A voltage map was acquired with Rhythmia during both sinus rhythm (SR) and induced VT with the support of a steerable long sheath (Agilis, St Jude Medical, St Paul, MN). Activation maps were created using the standard beat acceptance criteria (automatic) based on (1) CL variation, (2)electrocardiogram QRS morphology, (3) catheter motion, (4) electrogram stability, (5) catheter tracking quality, and (6) respiration gating. The confidence mask parameter was nominally set at 0.03 mV, which was manually lowered to be as close as possible to the noise threshold, to allow visualization of the entire circuit.14,15 In SR, all points within 2 mm of the surface were analyzed, and local abnormal ventricular activities (LAVAs) were manually annotated in areas with coexisting LAVA and far-field activity. Areas of scar and dense scar were defined as <0.8 and <0.2 mV.^{16,17} VT inducibility was assessed with 2 drive trains (600 and 400 ms) with up to 3 extrastimuli decremented to 200 ms (or ventricular refractory period) from the right ventricular apex after the creation of the activation map during SR. After the induction of VT, sustained VT was mapped and ablation was performed with the guidance of conventional activation and entrainment mapping. Regardless of VT termination with ablation, LAVA ablation was always subsequently performed with the endpoint of LAVA elimination.¹³ Radiofrequency energy was delivered using an irrigated 3.5-mm-tip ablation catheter (Thermocool SF catheter, Biosense Webster, Diamond Bar, CA), with a power of 35-50 W endocardially and 25-35 W epicardially. Where LAVA could be discerned to follow a distinct activation sequence on electroanatomical mapping (EAM), the earliest signals were targeted first. After ablation, the areas previously displaying LAVA were remapped. In the presence of residual LAVA, further radiofrequency ablation was performed. At the end of the procedure, induction of VT was repeated with programmed stimulation using the same protocol as before ablation.

Post hoc analysis

The 3D EAM was merged on the MDCT geometries on the Rhythmia system (Boston Scientific, Marlborough, MA)

using identifiable anatomic reference points (superior vena cava, inferior vena cava, left atrium, CS, aortic root, LV apex, and mitral annulus [MA] [3, 6, 9, and 12 o'clock]) to align both surfaces (Figure 1). The analyses were then performed using custom-built software in MATLAB. On MDCT data, a computed tomography (CT) channel was defined according to the following 3 criteria, as shown in Figure 2: (1) abnormal thickness (<5 mm), (2) thickness on both edges thinner than that inside the channel, (3) length longer than width.

CT channels were identified by a consensus of blinded analyses by 3 trained physicians (1 radiologist and 2 electrophysiologists). The contours of each CT channel were traced on the CT geometry.

On electroanatomical maps, a VT isthmus was defined as follows: (1) regions sequentially activated during the diastolic phase of VT, (2) confirmed by entrainment pacing¹⁸ or direct termination during ablation on the site with the diastolic potentials.

Additionally, the VT is thmus was divided into 3 portions based on the local activation time in the activation map in the present study; the first third of the diastolic phase is referred to as the entrance (early diastolic phase), the second third as the central isthmus (mid-diastolic phase), and the last third as the exit (late diastolic phase). Isthmuses and nearby edge zone areas were manually traced on the EAM geometry.

After registration, SR and VT maps, including electrophysiological isthmus segmentations, were projected on the CT geometry using a nearest-neighbor approach. This allowed automated comparison between electrophysiological findings and wall thickness measurements. Wall thickness and isthmus areas were directly compared with LAVA distributions. The spatial correlation between electrophysiological isthmuses and CT channels was analyzed.

Statistical analysis

Categorical data were expressed as numbers and percentages. Continuous data for normally distributed variables were expressed as mean \pm standard deviation and non-normally distributed data as median (25th–75th percentiles). Comparisons were performed with Student *t* test or Kruskal-Wallis analysis. Logistic regression analysis was performed to elucidate the factors predictive of CT channels associated with VT isthmuses. All tests were 2-tailed, and a *P* value of <.05 was considered statistically significant.

Results

Patient characteristics and characteristics of CT channels

The baseline characteristics of the 9 patients and CT channel characteristics are shown in Tables 1 and 2, respectively. Median (range) thickness was 2.4 (2.1–3.5) mm inside CT channels and 1.6 (0.9–2.2) mm on their edges (P < .0001). No channel was identified in regions thinner than 1 mm and no edge region was identified in regions thicker than 4 mm.

VT activation mapping and ablation

The characteristics of VT activation maps are shown in Table 3. VT was induced in all patients. In total, 32 different VTs (median 4 per patient) were observed, of which complete activation maps were acquired in 10 (mean $CL = 429 \pm 77$ ms). In 1 patient (patient 7), epicardial mapping was performed with a VT isthmus, since neither diastolic potentials during VT nor LAVAs during SR were observed endocardially. Median



Figure 1 Registration of computed tomography (CT) image on the 3-dimensional (3D) mapping system. Activation map acquired from the Rhythmia mapping system is merged on the geometry with the multidetector computed tomography model off-line. Identifiable anatomic reference points (superior and inferior vena cava, left atrium, coronary sinus, aortic root, left ventricular apex, and mitral annulus [3, 6, 9, and 12 o'clock]) were used as landmarks.



Figure 2 Computed tomography (CT)-defined wall thickness channels. CT channels are defined according to 3 criteria: (1) abnormal thickness (< 5 mm), (2) thickness on both edges thinner than that inside the channel, (3) length longer than width. (A) Multiple CT-channels (2-4 mm) are identified in the large anterior scar. (B) Multiple CT-channels (1-3 mm) between extremely thinned scar areas (<1mm) are distributed in the septal- to inferior-scar. (C) One discrete CT-channel (2-4 mm) is observed between the severely thinned lateral scar (<2mm) and the mitral annulus. (D) Relatively thicker CT-channels (3-5 mm) are distributed in severely thinned scar areas (< 2 mm).

length and width of VT isthmuses measured on the 3D EAM were 38 ± 15 mm. All VTs were terminated by ablation or mechanically terminated on the VT isthmus except for 1, which was overdrive-paced owing to poor hemodynamic tolerance. Complete LAVA elimination was not achieved in 1 patient (1/9, 11.1%) because of an extensive LAVA distribution. Mean procedure and ablation times were 280 ± 48 minutes and 57 ± 18 minutes, respectively.

CT thickness vs LAVA in SR

All but 1 patient (incessant VT) had a voltage map during the sinus rhythm prior to VT induction and ablation. In a total of 35,217 points, 1070 (3.0%), 4164 (11.8%), 4615 (13.1%), 4277 (12.1%), 3173 (9.0%), and 17,918 (50.9%) points were distributed in areas with WT of 0–1 mm, 1–2 mm, 2–3 mm, 3–4 mm, 4–5 mm, and normal thickness (WT >5 mm), respectively; out of these points, 336 (31.6%), 1113 (26.7%), 1358 (29.4%), 957 (22.4%), 475 (15.0%), and 922 (5.1%) showed LAVA potentials, respectively. One patient had a maximal

Table 1 Patient characteristics (N = 9)

proportion of LAVAs in 3-4 mm, 3 patients in 2-3 mm, 2 in 1-2 mm, and 2 in 0-1 mm.

CT thickness channels vs VT isthmuses

The relation between the wall thickness channels and VT isthmuses are demonstrated in detail in the Supplement table 1. Of the 10 VTs in which the VT circuit was fully characterized by activation mapping covering an entire CL, all VT isthmuses co-localized with CT channels. Out of the 41 CT channels identified in the population, 21 (51.2%) contained diastolic potentials during VT, including 13 (31.7%) with mid-diastolic potentials. These electrical VT isthmuses went through a single CT channels in 3 (30%) VTs, 2 CT channels in 2 (20%), 3 CT channels in 3 (30.0%), and 4 CT channels in 2 (20.0%) (Supplemental Table 1). However, all entrance, central, exit part of the VT-isthmus was covered by some of them. Therefore, channels defined by CT predict involvement in a critical part of the VT circuit with a

| Patient no. | Age | Sex | Scar location | EF | Procedure no. | HT | DM | DL | Smoking | ICD | Beta-blocker | Amiodarone |
|-------------|-----|-----|-------------------|----|---------------|----|----|----|-----------|-----|--------------|------------|
| 1 | 59 | М | Inferior, lateral | 25 | 3 | Y | N | Y | Y | Y | Y | Y |
| 2 | 29 | м | Anterior, lateral | 28 | 3 | Ν | Ν | Ν | Ν | Y | Y | Ν |
| 3 | 62 | М | Anterior, septal | 30 | 1 | Y | Ν | Y | Cessation | Y | Y | Y |
| 4 | 75 | М | Inferior, septal | 40 | 4 | Y | Ν | Y | Y | Y | Y | Y |
| 5 | 47 | F | Anterior, septal | 31 | 1 | Ν | Ν | Ν | Y | Y | Y | Ν |
| 6 | 48 | М | Anterior, septal | 30 | 2 | Ν | Ν | Y | Y | Y | Y | Y |
| 7 | 71 | М | Inferior, lateral | 40 | 4 | Y | Y | Y | Cessation | Y | Y | Y |
| 8 | 68 | М | Inferior, septal | 45 | 1 | Y | Ν | Y | Y | Y | Y | Ν |
| 9 | 72 | F | Inferior | 36 | 1 | Ν | Ν | Y | Y | Y | Y | Y |

DL = dyslipidemia; DM = diabetes mellitus; EF = ejection fraction; HT = hypertension; ICD = implantable cardioverter-defibrillator; N = no; Y = yes.

| Takigawa et al | Relationship | Between CT | Channel | and V | T Isthmus |
|----------------|--------------|------------|---------|-------|-----------|
| | | | | | |

| Table 2 | Computed tomograp | ohy channel character | istics | | | | | | |
|----------------|---|--|--------------------------|--------------------|------------------|-----------------------|----------------------------|--------------------------|-------------------------------|
| Patient no. | Thinned scar area (WT<5mm), cm ² | Severely thinned scar area (WT<2mm), cm ² | Number of CT channels | Length, mm | Width, mm | Area, cm ² | WT (channel center), mm | WT (channel edge), mm | Channel parallel to the MA |
| 1 | 121.81 | 44.71 | 4 | 37.8 (24.0-58.4) | 11.9 (10.0–17.5) | 1.93 (1.63-4.43) | 2.4 (2.2–3.4) | 1.9 (1.5–2.3) | 3 (75.0%) |
| 2 | 118.92 | 13.26 | 7 | 20.7 (17.6-26.1) | 7.9 (7.3–11.5) | 1.03 (0.88–1.74) | 3.5 (2.3–3.7) | 2.9 (2.1–3.1) | 4 (57.1%) |
| ŝ | 110.1 | 60.8 | 7 | 38.8 (31.4-62.0) | 14.0(9.2-32.0) | 1.46(1.23 - 12.0) | 2.3(1.9-3.5) | 1.3(0.9-1.7) | 4 (57.1%) |
| 4 | 46.4 | 20.2 | c | 17.7 (9.9–36.8) | 8.6 (7.9–9.0) | 1.59(0.90-1.92) | 2.1(1.0-2.5) | 0.8 (0.6–0.9) | 2 (66.7%) |
| 5 | 47.7 | 17.1 | 4 | 15.0 (11.0-21.7) | 5.1(3.4-9.8) | 0.90(0.54 - 1.34) | 2.3 (2.0-2.7) | 1.4(0.7-1.6) | 4 (100%) |
| 9 | 85.1 | 24.8 | 7 | 33.2 (30.0-44.9) | 16.5(10.9-19.9) | 1.75(1.55-3.58) | 3.0 (2.1-4.6) | 1.3(0.9-1.7) | 2 (28.6%) |
| 7 | 86.4 | 51.9 | 1 | 52.5 | 18.1 | 3.79 | 2.1 (2.1-2.1) | 0.7 (0.7-0.7) | 1(100%) |
| ∞ | 45 | 8 | 5 | 18.7 (15.6 - 22.6) | 7.2 (6.4–16.8) | 1.29(1.11 - 1.75) | 2.8 (2.3–3.5) | 2.0(1.9-2.4) | 3 (60.0%) |
| 6 | 54.9 | 36.3 | с | 36.8 (33.2-41.1) | 7.7 (7.0-44.6) | 1.76(1.11-2.78) | 1.7(1.2-2.1) | 0.6(0.6-0.9) | 2 (66.7%) |
| Median | 85.1 | 24.8 | 4 (3-7) | 30.0 (18.5-40.2) | 10.9(7.2 - 15.9) | 1.55(1.05-2.28) | 2.4(2.1-3.5) | 1.6 (0.9–2.2) | 24/41 (58.5%) |
| | (47.1 - 114.5) | (15.2 - 48.3) | | | | | | | |
| - to uo - | ar TM bac core d+bin | , aciboa se bodisso d | ofth 76th porcontilo | | | | | | |

sensitivity of 100% and a positive predictive value of 51.2% (Supplemental Table 2).

WT at the center of CT channels was always above 1 mm (Supplemental Figure 1A). WT on CT channel edges was always less than 4 mm (Supplemental Figure 1B). Examples of CT channels containing diastolic activity during VT are shown in Figure 3A/Video 1 and Figure 3B/Video 2. Table 4 compares the CT channel characteristics between those hosting diastolic activation during VT and those that did not. Univariate analysis identified 3 significant morphological predictors of diastolic activation during VT, 2 of which remained independent predictors on the multivariate analysis: longer CT channels (P = .04, odds ratio [OR] 1.05 [1.00–1.10]) and thinner (but >1 mm) CT channels (P = .03, OR 0.36 [0.14–0.90]). CT channels parallel to the MA was weakly associated (P = .07, OR 3.93 [0.89-17.42]). A WT at CT channel center of 1-4 mm and a length >2 cm predicted an electrophysiological VT isthmus with 86% sensitivity and 60% specificity. CT channels implicated in VT also had a higher proportion of LAVA, although the difference did not reach statistical significance (P = .09).

Outcome during follow-up

During a mean follow-up of 19.7 ± 15.5 months, 2 patients had VT recurrence (patients 3 and 6). In patient 3, the index procedure failed to achieve complete LAVA elimination and a post hoc analysis of CT channel vs VT isthmus showed that some of the CT channels had not been completely transected. During the redo procedure, a VT with a different morphology from the index procedure was successfully mapped and terminated at a site with a mid-diastolic potential corresponding with 1 of the CT channels, although using a different exit from the index VT. In patient 6, the index procedure ended with a complete LAVA elimination. The post hoc analysis of CT channel vs VT isthmus showed that all regions matched to CT channels were well ablated. As endocardial LAVAs were completely ablated in the index procedure, an epicardial approach was prepared for the redo procedure. The redo procedure identified 2 VTs with different morphologies from those observed during the index procedure, 1 of which was mappable. The epicardial map demonstrated mid-diastolic potentials at a site immediately opposite to the CT channel identified on the endocardium and the VT was terminated at this site. Residual epicardial LAVAs identified in this area were all eliminated and no endocardial ablation was required. No recurrence was seen afterward in these 2 patients.

Discussion

computed tomography; MA = mitral annulus; WT = wall thickness.

Ш Б This study is, to our knowledge, the first to compare the distribution of CT-defined anatomical channels with VT isthmuses. The main findings are that (1) CT wall thickness maps of the MI scar are feasible and identify CT channels; (2) these CT channels are thin, with edges thinner by at least 1 mm; (3) electrical VT is thmuses co-localize with 1 or more of the CT channels in 100%, and 50% of CT channels

| Table 3 | VT and ac | ute ablation | result | | | | | | | |
|----------------|----------------------|--------------------|------------|--------------|-----------------------------|--------|-------------------------------|-------------------|-----------------------------|-------------------------|
| Patient no. | No. of induced VT | No.of mapped VT | Morphology | VT CL, ms | Mapped VT, no. of points | Loop | Isthmus parallel to the MV | VT termination | Endpoint (LAVA elimination) | Post-RF inducibility |
| 1 | 4 | 1 | RBBB | 508 | 10,546 | Dual | Y | Y | Complete | N |
| 2 | 7 | 1 | RBBB | 275 | 5875 | Dual | Y | Y* | Complete | Ν |
| 3 | 6 | 2 (VT1) | RBBB | 393 | 5233 | Single | Ν | Y* | Partial | Rapid VT (200bpm) |
| | | (VT2) | RBBB | 446 | 12,397 | Dual | Ν | Y | | |
| 4 | 1 | 1 | RBBB | 458 | 8368 | Single | Y | Y | Complete | Ν |
| 5 | 2 | 1 | LBBB | 379 | 890 | Dual | Y | Ν | Complete | Ν |
| 6 | 2 | 1 | LBBB | 521 | 4040 | Dual | Ν | Y | Complete | Ν |
| 7 | 1 | 1 [†] | LBBB | 410 | 53,085 | Dual | Y | Y | Complete | Ν |
| 8 | 5 | 1 | RBBB | 426 | 9151 | Dual | Y | Y* | Complete | Ν |
| 9 | 4 | 1 | RBBB | 492 | 6530 | Single | Y | Y | Complete | Not tested |

CL = cycle length; LAVA = local abnormal ventricular activity; LBBB = left bundle branch block; RF = radiofrequency; RBBB = right bundle branch block; VT = ventricular tachycardia.

*Mechanical termination on the VT isthmus.

[†]VT using an epicardial circuit.

correspond to VT isthmuses; (4) the CT channels hosting VT isthmuses may have some morphological characteristics.

CT channel vs VT isthmus

In the present study, we found that all VT isthmuses used 1 or 2 CT channels and that 51.2% of CT-defined channels hosted a VT isthmus (sensitivity of 100% and positive predictive value of 51.2%) (Supplemental Table 2).

Previous reports have shown that the scar extent on late gadolinium–enhanced CMR is significantly associated with VT inducibility and prognosis in patients with structural heart disease.^{19,20} In addition, scar transmurality, defined as the ratio of postinfarct scar thickness to LV WT has been associated with electrogram characteristics on EAM.^{1–3,21,22} The utility of both MDCT and CMR in VT ablation has been previously reported,^{7,23} and MDCT has been shown to reliably identify areas of low voltage,



Figure 3 Computed tomography (CT) channels vs ventricular tachycardia (VT) activation map. VT activation map was merged on the wall thickness (WT) map in (A) and (B). A: Clinical monomorphic VT in 59-year-old man with inferolateral infarction. One CT channel covered diastolic activation as shown in 3 electrograms (EGMs), where CT channel is composed of 2-4 mm WT areas bredered by severely thinned areas (<2 mm). VT was terminated during ablation in this location, and the same VT was not induced after ablation at this site. B: Recurrent monomorphic VT in 71-year-old man with inferolateral infarction. Complete local abnormal ventricular activity elimination with noninducibility was achieved endocardially at the previous session. CT channel corresponded with epicardial VT isthmus showed a WT of 2-4 mm bordered by severely thinned scar (<2 mm) area and anatomical obstacle (MA = mitral annulus). Epicardial EGMs on the isthmus are shown in the figure.

Takigawa et al Relationship Between CT Channel and VT Isthmus

| Table 4 CI channel character | istics associated with VI istnmu | Ises | | | |
|---|--|--|----------------------------|-------------------------|---------------------------------------|
| CT channel characteristics | Not hosting diastolic activity during VT ($n = 20$) | Hosting diastolic activity during VT (n = 21) | Univariate P value | Multivariate P value | OR (95% CI) |
| Length, mm Width, mm Area, cm ² | 21.2 (17.3–36.8) 9.0 (6.7–16.5) 1.49 (1.00–1.75) | 33.2 (25.7–43.0) 11.5 (7.8–15.5) 1.69 (1.17–2.55) | .036 .35 .3 | .04 | 1.05 (1.00–1.10) |
| Parallel to the MA, n (%) Isthmus central thickness, mm Isthmus edge thickness, mm Distribution of the LAVA on the | 8 (40.0%) 2.7 (2.3–3.7) 1.9 (0.9–2.6) 13.2 (5.7–42.2) | 16 (76.2%) 2.2 (1.9–2.9) 1.4 (0.9–1.7) 38.6 (14.8–57.4) | .027 .042 .21 .09 | .07 .03 | 3.93 (0.89–17.42) 0.36 (0.14–0.90) |

 Table 4
 CT channel characteristics associated with VT isthmuses

Length, width, area, isthmus central thickness, isthmus edge thickness, and LAVA distribution are all described as median (25th-75th percentiles). CT = computed tomography; LAVA = local abnormal ventricular activity; MA = mitral annulus; VT = ventricular tachycardia.

identified using a 3D mapping system.^{7,23} The present study provides the further possibility that CT-WT channels can be used to identify the VT isthmus with high sensitivity. In post-MI scar, the thinnest parts (channel edges) are likely to have no or very few surviving bundles. They could therefore act as zones of block, or pseudo-block owing to relatively slower transverse conduction, whereas the relatively thicker channels between the thinnest areas may host residual slowly conducting bundles.

Although MDCT may identify VT isthmuses, it does not identify whether the channel should be approached from the endocardium vs the epicardium. In patient 6, all the preprocedure CT channels appeared to have been ablated using the conventional approach, yet the patient had VT recurrence requiring an epicardial approach. Further, in patient 7, VT with an epicardial isthmus was observed even though no LAVAs were identified endocardially. Although the endocardial approach is usually sufficient post myocardial infarction, an epicardial approach may be also taken into consideration for redo procedures where transection of all channels was achieved in the index procedure.

CT channel characteristics more associated with mapped VT isthmuses

As some rapid or unstable VTs were not successfully mapped, we were unable to demonstrate a relationship between the VT isthmuses and CT channels in these VTs. Nevertheless, some morphological characteristics were statistically associated with mapped VT isthmuses. Thinner, longer channels and channels parallel to the MA were more frequently functional (associated with a mapped VT isthmus). However, even long CT channels are not systematically predictive of VT isthmuses, particularly in thicker tissue. This observation fits well with another observation in our study, that LAVAs are much less frequent when wall thickness is above 4 mm. In these regions, myocardium is healthier, most likely associated with more normal conduction properties, and therefore less likely to participate in a VT isthmus. These morphological characteristics may be useful to guide ablation of the higher-risk CT channels. However, more data should be collected; although the channel morphologies were different between those supporting VT and those not, there was still significant overlap between groups. The association between VT isthmuses and channels parallel to the MA requires further corroboration owing to the weak statistical significance and lack of a theoretical explanation for the finding, although one could speculate that channels bordered by basal scar and the MA support VT more frequently because the MA is a complete anatomical insulator. This is of major importance as we cannot rule out that some CT channels are functional VT isthmuses for VTs that were simply not induced in this study. A practical approach (aiming at the best single-procedure success rate) could target all CT channels in order to ensure the most comprehensive ablation of the VT substrate.

Relationship between wall thickness and LAVAs

The present study also describes the distribution of LAVAs in the scar area using a high-resolution mapping system. A total of 20%–30% of all points in the WT \leq 4 mm had LAVAs. Indeed, LAVAs were overall most frequently identified in the thinnest WT area (0-1 mm). However, individually, LAVA distribution was highest in this thinnest area only in 2 patients, and CT channels used as VT isthmus were never found in these thinnest regions. These results suggest that LAVA distribution in the thinnest areas (<1 mm) may not be associated with the maintenance of VT despite the high prevalence of LAVAs. Although complete LAVA elimination is associated with better outcomes, 12 LAVA elimination in the thinnest areas may not always be necessary to avoid VT recurrence (at least in slow VT mapped in the present study). Although more detailed characteristics of LAVA such as voltage and/or delay may be associated with the maintenance of VT, LAVA distribution in SR itself may be not enough to narrow the ablation target.

Clinical implications

CT scans are easy to obtain, reproducible from center to center, and of very consistent quality, allowing for high spatial resolution assessment of the post-MI scar. Wall thickness maps describe CT channels that host 100% of VT isthmuses. This information—available before the procedure—refines the substrate definition, is highly sensitive, and could be more specific than the 3D EAM of the substrate. By providing more specific and clearly defined ablation targets, this preprocedural diagnostic phase could help the operator to use a more focused ablation strategy and shorten traditionally long VT ablation procedures.

Study limitations

The first limitation of the present study is that not all VTs were mappable, and therefore the VTs mapped may not be representative of the whole population of VTs. VTs were not always sufficiently stable or tolerable for complete mapping. However, sufficient mapping data were acquired per patient and CT channel to allow for valid statistical analyses. Another limitation is related to the potential misregistration between imaging and electroanatomical mapping geometries. This aspect was partly addressed by using state-of-the-art technologies embedded in 3D EAM, and did not prevent identification of matching CT channels and VT isthmuses. However, the geographical compatibility between the CT image and 3D EAM should be prospectively examined. Third, although the concept is likely to be similar in faster or unstable VTs, this is not proven, as the findings are derived from stable slower VTs. Also, the applicability to nonischemic VTs requires further assessment, as the mechanism and distribution of scars (substrates) are different. Fourth, especially in patients with ICD storm or incessant VTs, renal dysfunction may prevent contrast CT acquisition and therefore may limit generalizability of these results to sicker patients with VT. Finally, the efficacy and safety should be compared with a standard ablation strategy.

Conclusion

CT scan wall thickness maps identify CT channels that host VT isthmuses consistently. Half of the CT-defined channels are associated with the critical isthmus of mapped VT. If not all CT channels are functional VT isthmuses, perhaps owing to VT noninducibility, longer and thinner (but >1 mm) CT channels parallel to the mitral annulus are more frequently associated with VT isthmuses. The integration of these 3D models describing clear and focused targets could help to shorten VT ablation procedures, and potentially improve outcomes, but the clinical impact of this approach needs to be tested in further prospective trials.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019. 06.012.

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1939 **6-3.** Ablation of CT-derived wall thickness channels in post-infarction ventricular tachycardia:

1940 comparison to conventional LAVA elimination strategy.

1941

1942 Background and purpose

1943 From the result of the second study (Chapter 6-2), we have proved that the CT-derived channels are associated with 1944 VT-isthmuses. For VT ablation, LAVA elimination has been used as a standard strategy in our institution. Although 1945 LAVA elimination is an effective VT ablation strategy, it is lengthy and poorly standardized. Based on these facts, we 1946 hypothesized that CT-derived wall thickness channels ablation strategy may be more specifically target the potential 1947 VT is thmuses and may shorten the procedure time with a similar outcome from the conventional LAVA elimination 1948 strategy in ischemic VT. The endpoint of CT-channel ablation is loss of local capture on the CT-channels, whereas 1949 that of LAVA ablation is complete elimination of LAVA potentials as described in the Figure 6-3-1. We aimed to 1950 prove this.

1951 Methods and results

Of 214 consecutive patients received CA for ischemic VT between 2010 and 2017, 25 patients were treated with a CT-channel based ablation strategy. 25 patients treated with LAVA elimination were matched in a 1:1 ratio based on propensity scores with similar characteristics (age, gender, LVEF, risk factors, therapies, arrhythmia burden, catheter mapping techniques), which resulted in two balanced groups of 25 patients each. Outcome, procedure time, fluoroscopy time, complication rate, were compared between these two groups.



1957





- ablation group, which was significantly shorter than that in LAVA-ablation group (median 61.5min, P<0.0001.).
- 1962 Although ablation time was similar between two groups (median 30 [23-45] min in CT-ablation group vs median 39
- 1963 [22-54]min in LAVA-ablation group, P=0.34), procedure time was remarkably shorter in CT-ablation group (190
- 1964 [165-215] min) compared to the LAVA-ablation group (255 [230-300], P<0.0001). CT-ablation reduced the median
- 1965 procedure time by 25%. Complication rate was similar between the two groups (one cardiac tamponade in LAVA-

| 1966 | ablation | group, | and | one | stroke | in | CT-ablation | n group.) |
|------|-----------|----------------------|-----------------|------------------|------------|------------|---------------|-----------|
| | Procedura | al characteristics a | and acute proc | cedural outcomes | LAVA-g | roup | CT-group | P-values |
| | Acute out | tcome | | | | | | |
| | Total ma | apping time (regis | stration time), | min | 61.5 [39.8 | -83.8] | 12 [9-16] | < 0.0001 |
| | Termina | tion during VT | | | 11/25 (44 | .0%) | 8/25 (32.0%) | 0.56 |
| | Procedu | re time, min | | | 255 [230- | -300] | 190 [165-215] | < 0.0001 |
| | Ablation | n time, min | | | 39 [22- | 54] | 30 [23-45] | 0.34 |
| | Complica | tion | | | 1 (4.0% | %) | 1 (4.0%) | 1 |
| | LAVA eli | mination | | | | | | < 0.0001 |
| | Complet | te LAVA eliminat | ion | | 20 (80.0. | .0%) | 5 (20.0%) | |
| | Residual | l LAVA (+) or No | t-checked | | 5 (20.0 | %) | 20 (80.0%) | |
| | Not-che | cked | | | 0 (0% | () | 5 (20.0%) | |
| | VT induc | ibility | | | | | | |
| | VT indu | ction performed | | | 21 (84.0 | 0%) | 22 (88.0%) | 1 |
| | Negative | e VT induction | | | 17/21 (81 | .0%) | 20/22 (90.9%) | 0.41 |

1967

1968 Table 6-3. Comparison of Procedural characteristic and acute results

1969

1970 VT-recurrence at 1 year was observed in 5/25 (20.0%) in the LAVA-ablation group and 6/25 (24.0%) in the CT1971 ablation group (P=1.0000). VT-recurrence free survival rate was similar between the two group (P=0.62) as described
1972 in the Figure 6-3-2.

1 Yr follow up

| Follow-up | LAVA-group | CT-group | P-values | |
|--------------------------|------------|-----------|----------|--|
| VT-recurrence at 6 month | 4 (84.0%) | 5 (80.0%) | 1 | |
| VT-recurrence at 1yr | 5 (80.0%) | 6 (76.0%) | 1 | |





1975 Figure 6-3-2. Follow-up after the VT-ablation

1976

1977 Summary and conclusion

1978 Complete LAVA elimination was frequently not achieved in the CT-ablation group, but post-ablation VT

1979 inducibility and VT-recurrence rate at 1 year were similar between two groups. Substrate-based ablation targeting

1980 CT-defined channels shortens VT ablation procedures by over 20% with similar outcomes as compared to the

1981 conventional strategy targeting the electrophysiological substrate.

- 1982
- 1983

1984 Manuscript is in submission

1985

1986 Ablation of CT-derived wall thickness channels in post-infarction ventricular tachycardia: comparison to

- 1987 conventional LAVA elimination strategy
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| 1 | Ablation of CT-derived wall thickness channels in post-infarction ventricular tachycardia: |
|-----|--|
| 2 | comparison to conventional LAVA elimination strategy |
| 3 | |
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| 23 | |
| 24 | Word count: 4206 words |
| 25 | BACKGROUND: |
| | |

| 26 | Although LAVA | elimination is a | an effective | VT ablation | strategy, it is | lengthy and | poorly standardized. |
|----|---------------|------------------|--------------|-------------|-----------------|-------------|----------------------|
| | 0 | | | | | | |

27

| 28 | PURPOSE: We compared strategies of ablation based on CT-derived wall thickness vs elimination of local |
|----|--|
| 29 | abnormal ventricular activities (LAVAs) in ischemic VT. |

30

31 METHODS:

- 32 Propensity score matching was used in consecutive patients with ischemic VT ablation using either a LAVA
- 33 elimination strategy (N=189) or CT channel ablation (N=25) to identify 25 pairs of patients with similar
- 34 characteristics (age, gender, LVEF, risk factors, therapies, arrhythmia burden, catheter mapping techniques).
- 35 In the CT group, anatomy of the atria and/or aorta were briefly mapped to register CT-meshes to
- 36 3D-electro-anatomical maps (3D-EAM). In both groups, the ablation strategy involved targeting any
- 37 mappable induced VT, in addition to targeting LAVA or CT channels.
- 38
- 39 **RESULTS:** In the CT group, a median of 3 [2-4.3] CT channels were found, with length 28.0 [23.5-33.4] mm,
- 40 width 10.4 [8.7-12.7] mm, and area 347 [258-559] mm². LV thickness was 3.1 [2.5-3.8] mm within channels,
- 41 and 2.2 [1.7-2.9] mm on their borders. Despite a similar ablation time (median 39 [22-54] min vs. 30
- 42 [23-45]min in LAVA vs. CT, P=0.34), the median procedure time was markedly shorter in the CT group (255
- 43 [230-300]min vs 190 [165-215]min, (P<0.0001). VT inducibility, tested in >80% at the end of the procedure,
- did not differ between LAVA and CT groups (19.0% vs 9.1%, P=0.41). Complication rate was similar (1
- 45 stroke in CT and 1 tamponade in LAVA). 1-yr VT recurrence did not differ (24% in LAVA vs. 24% in CT,
- 46 P=1.00).
- 47

48 CONCLUSION:

- 49 Substrate-based ablation targeting CT-defined channels shortens VT ablation procedures by over 20%, with
- 50 similar outcomes as compared to a conventional strategy targeting electrophysiological substrate.
- 51

- 52 Keywords; ventricular tachycardia, contrast-enhanced multidetector computed tomography, wall thickness,
- 53 isthmus
- 54

Disclaimentiality and not to be functioned and its contents are seed.

55 Introduction

| 56 | Substrate ablation in ischemic ventricular tachycardia (VT) patients has been reported as an effective strategy |
|----|---|
| 57 | to treat VT ¹⁻⁵ . We have also reported long-term outcomes of LAVA ablation, and complete LAVA elimination |
| 58 | was strongly associated with a better long-term outcome ⁶ . However, especially in patients with extensive scar, |
| 59 | eliminating all LAVAs is time consuming and sometimes difficult to achieve. On the other hand, we have |
| 60 | reported data that based on CT-imaging, areas of both high wall thickness>4mm and low wall thickness < |
| 61 | 1mm in the scar did not often contribute to the critical VT-isthmus in ischemic cardiomyopathy ^{7,8} . Areas of |
| 62 | high wall thickness usually demonstrate relatively few LAVA ⁹ , which are therefore less likely to represent the |
| 63 | slow conducting VT-isthmus. Additionally, the areas of thinnest scar <1mm still harbour LAVAs, but these |
| 64 | LAVAs may signify areas of block rather than critical slow conduction. We have reported that CT-channels |
| 65 | derived from CT-imaging can describe the VT-isthmus with high-sensitivity ⁷ . Therefore, in the present study, |
| 66 | we aimed to study if CT-channel based ablation could reduce ablation time without lowering outcome rates. |
| 67 | |
| 68 | METHODS |
| | |

69 Patient Selection

- 70 From 2010 to 2017, a total of 214 consecutive patients received catheter ablation for ischemic VT. Of that
- 71 cohort, 25 patients with a CT-channel based ablation strategy and 25 with a LAVA-ablation strategy, were
- 72 matched in a 1:1 ratio based on propensity scores with similar characteristics (age, gender, LVEF, risk factors,
- 73 therapies, arrhythmia burden, catheter mapping techniques), which resulted in two balanced groups of 25
- 74 patients each.

75 Image Acquisition and segmentation

76 Contrast-enhanced MDCT was performed with a 2 × 192 detector dual-source scanner (Somatom Force,

- 77 Siemens Healthcare, Forchheim, Germany), 1 to 3 days prior to the ablation procedure. Images were acquired
- 78 in mid-diastole using prospective ECG-triggering during an expiratory breath-hold, with tube voltage and
- 79 current adapted to patient morphology. Acquisition was performed in the arterial phase after the injection of a
- 80 dual-phase bolus of iodinated contrast agent, i.e. 60mL of 100% contrast at the rate of 5 ml/s, followed by
- 81 80mL of 50/50% contrast/saline at the same rate.
- 82 Image processing was performed by 2 trained technicians using the MUSIC platform (Liryc, Université de
- 83 Bordeaux, Bordeaux & INRIA, Sophia Antipolis, France), as described previously⁹⁻¹². Briefly, the cardiac
- 84 chambers, ventricular epicardium, ascending aorta, and coronary sinus (CS) were segmented
- 85 semi-automatically¹⁰, and ventricular endocardium automatically. WT was automatically computed from
- 86 endo- and epicardial contours. We used 5-mm as a cutoff for significant myocardial thinning based on
- 87 previously reported MDCT values of WT in a healthy population¹². A 3-dimensional patient-specific model
- 88 comprising all anatomical information was generated and exported in Matlab (The Mathworks, Inc., Nattick,
- 89 MA) for subsequent post-hoc integration with electroanatomical geometries.
- 90 Electrophysiological Study
- 91 Two 6-French decapolar catheters were inserted from the right femoral vein and placed in the CS and the RV.
- 92 The LV endocardium was accessed using a trans-septal approach or trans-aortic approach or both. Pericardial
- 93 access was obtained via a percutaneous subxiphoid puncture if required^{5,13}. VT inducibility was usually
- 94 assessed before and after ablation with 2 drive trains (600 and 400ms) with up to 3 extrastimuli decremented
- 95 to 200ms (or ventricular refractory period) from the RV apex. When VT was induced, sustained VT was
- 96 mapped and ablation was performed with the guidance of conventional activation and entrainment mapping.
- 97 Regardless of VT termination with ablation, additional ablation was performed following one of two possible
- 98 strategies; LAVA-ablation or CT-channel guided ablation. RF power was limited to 35-50W endocardially
- 99 and 25-35W epicardially. Where LAVA could be discerned to follow a distinct activation sequence on EAM,
- 100 the earliest signals were targeted first. After ablation, the areas previously displaying LAVA were remapped.
- 101 In the presence of residual LAVA, further radiofrequency ablation was performed. Induction of VT post
- 102 ablation was repeated with programmed stimulation using the same protocol as before ablation.

103 CT-channel guided ablation vs LAVA ablation

- 104 In the CT-channel guided ablation group, the 3D-electro-anatomic mapping (EAM) geometry was merged on
- 105 the MDCT geometry using identifiable anatomic reference points (Superior vena cava, inferior vena cava, left
- atrium, CS, aortic root, LV apex, and mitral annulus (MA) [3, 6, 9, and 12 o'clock]) to align both surfaces
- 107 (Figure 1). A complete LV map was not always required. On MDCT data, a CT-channel was defined
- 108 according to the following 3 criteria, as described in the previous study⁷.
- 109 1. Abnormal thickness (<5 mm)
- 110 2. Thickness on both borders thinner than inside the channel.
- 111 3. Length greater than width.
- 112 CT-channels were identified by a consensus of blinded analyses by 3 trained physicians (one radiologist and
- 113 two electrophysiologists). The geometry of each CT-channel was calculated using the MUSIC system. The
- 114 contours of each CT channel were traced on the CT geometry. These CT-channels were targeted for ablation
- 115 with a primary endpoint of loss of local capture. Remapping was not always required.
- 116 In contrast, in the group undertaken using a conventional approach, ablation was always subsequently
- 117 performed after the termination of VT with an endpoint of LAVA elimination^{5,6}, even in cases where the
- 118 CT-image was registered on the 3D-EAM. VT-inducibility was examined as a secondary endpoint; however,
- 119 additional ablation was not performed even if VT was induced after the end-point of each strategy had been
- 120 reached.
- 121 Outcome, procedure times, fluoroscopy times, and complication rates were compared between these two
- 122 groups.
- 123

124 Statistical Analysis

- 125 Categorical data were expressed as numbers and percentages. Continuous data for normally distributed
- 126 variables were expressed as mean±SD and non-normally distributed data as median (25th-75th percentiles).
- 127 Comparisons were performed with Student's t tests or Kruskal-Wallis analysis. Logistic regression analysis

128 was performed to elucidate the factors predicting CT-channels associated with VT isthmuses. All tests were

- 129 2-tailed, and a P value of <0.05 was considered statistically significant.
- 130
- 131 RESULTS
- 132 Patient characteristics
- 133 Table 1 compares baseline characteristics of the matched patients (25 pts with CT-channel ablation vs 25 pts
- 134 with LAVA ablation). As shown in the figure, no significant differences in the background characteristics
- 135 were seen between the two groups. The geometry of the CT-channels in the CT-ablation group is described in
- 136 Table 2. A median of 3 [2-4.3] CT channels was found, with length 28.0 [23.5-33.4] mm, width 10.4
- 137 [8.7-12.7] mm, and area 347 [258-559] mm². LV thickness was 3.1 [2.5-3.8] mm within channels, and 2.2
- 138 [1.7-2.9] mm on their borders.
- 139 VT-induction
- 140 Details of VTs are shown in Table 3. VT inducibility was tested after mapping, or VTs were mechanically or
- simultaneously induced during substrate mapping in all patients except in one patient in the LAVA-group
- 142 because of hypokalemia. Although median VT cycle length (CL) was similar between the two groups
- 143 (P=0.96), VT was more frequently observed in patients in the LAVA group (1 [1-2] in the CT-group vs 2
- 144 [2-3.5] in the LAVA-group, P=0.02). A complete VT activation map was created in 5/25 (20.0%) in the
- 145 CT-ablation group and 7/25 (28.0%) in the LAVA-ablation group (P=0.74).
- 146 Acute result

| 147 | Median total | l mapping time was | 12 minutes in the C? | Γ-ablation group, | which wa | as significantly | shorter th | nan that |
|-----|--------------|--------------------|----------------------|-------------------|----------|------------------|------------|----------|
|-----|--------------|--------------------|----------------------|-------------------|----------|------------------|------------|----------|

- 148 in the LAVA-ablation group (median 61.5min, P<0.0001.) as described in Table 4. VT termination during
- 149 ablation was observed in 8/25 (32.0%) in the CT-channel group and in 11/25 (44.0%) in the LAVA-ablation
- 150 group (P=0.56). The wall thickness of the termination site was 1-2mm in one patient, 2-3mm in 4 patients and
- 151 3-4mm in 3 patients.
- 152 Although complete LAVA elimination was confirmed in 20/25 (80.0%) in the LAVA-ablation group, it was
- 153 confirmed only in 5/25 (20.0%) in the CT-ablation group (P<0.0001). VT induction was performed after
- 154 ablation in 21/25 in the LAVA-ablation group and in 22/25 in the CT-ablation group, and VT-inducibility was
- similar between the two groups (P=0.70). Complication rates were similar between the two groups (one
- 156 cardiac tamponade in the LAVA-ablation group, and one stroke in the CT-ablation group.) Although ablation
- 157 time did not show a significant difference between the two groups (median 30 [23-45] min in the CT-ablation
- 158 group vs median 39 [22-54]min in the LAVA-ablation group, P=0.34), procedure time was markedly shorter
- 159 in the CT-ablation group (190 [165-215] min) compared to the LAVA-ablation group (255 [230-300],
- 160 P<0.0001). The CT-ablation group demonstrated a 25% reduction in median procedure time.

161 Follow-up and repeat procedure

- 162 Figure 2 demonstrates the follow-up data. VT-recurrence at 6months was observed in 4/25 (16.0%) in the
- 163 LAVA-ablation group and in 5/25 (20.0%) in the CT-ablation group (P=1.000). VT-recurrence at 1 year was
- 164 observed in 5/25 (20.0%) in the LAVA-ablation group and in 6/25 (24.0%) in the CT-ablation group
- 165 (P=1.0000). In the LAVA ablation group, complete LAVA elimination was achieved in 2/5 (40.0%) patients

| 166 | with VT recurrence and in | 18/20 (90.0%) | patients without | VT recurrence. | VT | non-inducibility | was achieved |
|-----|---------------------------|---------------|------------------|----------------|----|------------------|--------------|
|-----|---------------------------|---------------|------------------|----------------|----|------------------|--------------|

- 167 at the end of the procedure in 2/5 (40.0%) patients with VT-recurrence and in 15/20 (75.0%) patients without
- 168 VT-recurrence. In the CT-ablation group, complete LAVA elimination was confirmed in 1/6 (16.7%) patients
- 169 with VT-recurrence and in 4/19 (21.1%) patients without VT-recurrence. VT non-inducibility was achieved at
- 170 the end of the procedure in 4/6 (66.7%) patients with VT-recurrence and in 16/19 (84.2%) patients without
- 171 VT-recurrence. VT-recurrence free survival rate was similar between the two groups (P=0.62).
- 172
- 173

174 **DISCUSSION**

- 175 This is to our knowledge, the first study to compare VT ablation strategies between conventional
- 176 LAVA-ablation and CT-channel ablation.
- 177 The main findings are that
- 178 1. Mapping time and procedure time were significantly shorter in the CT-group.
- 179 2. In the CT group, a median of 3[2-4.3] CT channels were found, with median length 28.2mm,
- 180 width 10.3mm, and area 347mm².
- 181 3. Complication rates were similar between the two groups.
- 182 4. Complete LAVA elimination was frequently not achieved in the CT-ablation group, but
- 183 post-ablation VT inducibility and VT-recurrence rate at 1 year were similar between the two
- 184 groups.

185 5. VT-free survival rate was similar between the two groups.

| 187 | Potential | of | CT-channel | ablation |
|-----|------------|-----|-------------------|----------|
| 107 | 1 otentiai | UI. | CI-channel | ablation |

- 188 The result in the present study demonstrates that CT-channel ablation may reduce procedure time
- 189 whilst maintaining a successful outcome and without increasing complications. Ablation of
- 190 CT-channels derived from the wall thickness distribution may be an optional tool added to a conventional
- 191 substrate ablation strategy. In the previous paper⁷, we reported the possibility that CT-wall thickness channels
- 192 can be used to identify VT isthmuses with high sensitivity. In post MI scar, the thinnest parts (channels
- 193 border) are likely to have no or very few surviving bundles. They could therefore act as zones of block
- 194 (functional or not) or pseudo-block, because of relatively slower transverse conduction¹⁴, whereas the
- 195 relatively thicker channels between the thinnest areas possibly host residual slowly conducting bundles.
- 196 Additionally, we have reported that some morphological channel characteristics (thinner but > 1mm and
- 197 longer) are statistically associated with functional isthmuses. In thick WT areas, the myocardium is healthier,
- 198 more likely to be associated with more normal conduction properties, and therefore less likely to participate in
- 199 a VT isthmus. However, these morphological characteristics of VT isthmuses were characterized based on
- 200 mappable VTs with slower CLs. This is of importance as we cannot exclude the possibility that some CT
- 201 channels are functional VT isthmuses for VTs that were simply not mapped during the procedure. Through
- 202 CT-channel ablation we could achieve high negative VT inducibility as an endpoint, similar to that of the
- 203 conventional LAVA elimination strategy. Thus CT-channel ablation may be more useful in patients with

| 204 | unmappable VTs as some CT channels may be functional and host unmappable VTs. A practical approach |
|-----|--|
| 205 | (aiming at the best single procedure success rate) could target all CT channels in order to ensure the most |
| 206 | comprehensive ablation of the VT substrate. |
| 207 | |
| 208 | However, this approach also results in extensive ablation to eliminate all substrate. Therefore, not only the |
| 209 | ablation time but also the procedure time are extended. This is also apparent when we compare the primary |
| 210 | result of LAVA ablation using a standard ablation catheter with a conventional mapping system ⁵ to the |
| 211 | long-term outcome of LAVA ablation procedures using multipolar catheters with a high-density mapping |
| 212 | system ⁶ . In the former study published in 2012, the total procedure time and ablation time was 148+/-73 min |
| 213 | and 23+/-11 min ⁵ . Conversely, in the latter study published in 2018, the total procedure time and ablation time |
| 214 | was 248+/-78 min and 36+/-20 min ⁶ . Although improvements in the mapping system and catheters |
| 215 | significantly increase the sensitivity to detect substrate, specificity has not been addressed. Not all the |
| 216 | potential substrate will be involved in VT initiation or maintenance, and ablating abnormal tissue that is not |
| 217 | actively participating in VT perpetuation could potentially create new areas of block/decrement that may |
| 218 | predispose to new VT circuits. Recent developments in this field are focused on improving the specificity of |
| 219 | VT-substrate detection which can be involved in the VT circuit, whilst maintaining high sensitivity. For |
| 220 | example, the significance of decrement evoked potentials in VT ablation has been reported ^{19,20} . In this VT |
| 221 | ablation strategy, the tissue was systematically stressed with extra stimuli when late potentials or |
| 222 | multicomponent potentials were identified, and only potentials with decremental properties were targeted. |

- 223 Mid-term outcomes of this limited focused mechanistic ablation strategy using extra stimuli are in keeping
- 224 with the current ablation outcomes described in the published data. CT-channel guided ablation may be
- another potential approach to achieve this goal.
- 226 Clinical implications
- 227 CT scans are easy to obtain, reproducible between centers and of consistent quality, allowing for high spatial
- 228 resolution assessment of post MI scar. Ablation strategies targeting CT-channels provide similar success rates
- 229 to LAVA-ablation, reducing procedure time by more than 20% without increasing complication rates.
- 230 Study limitations
- 231 The small sample is a limitation of the present study. A further limitation is related to potential
- 232 mis-registration between imaging and EAM geometries. This aspect was partly addressed through use of the
- 233 registration technologies embedded in the3D-EMS, and did not prevent identification of matching CT
- channels and VT is thmuses. The findings in this study may be applicable only to mappable slow VTs.
- 235

236 CONCLUSION

- 237 Substrate-based ablation targeting CT-defined channels shortens VT ablation procedures by over 20% with
- 238 similar outcomes as compared to a conventional strategy targeting the electrophysiological substrate.
- 239
- 240
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328 Table 1. Patient Characteristics (N=25)

| | LAVA-group | CT-group | |
|---|----------------|----------------|----------|
| | (n=25) | (n=25) | P-values |
| Age, yrs | 69 [53.5-75.0] | 69 [56.9-75.3] | 0.85 |
| Sex, male | 22 (88.0%) | 22 (88.0%) | 1 |
| LVEF, % | 33 [29-45.5] | 33 [30-45] | 0.88 |
| HT | 15 (60.0%) | 17 (68.0%) | 0.77 |
| DM | 3 (12.0%) | 5 (20.0%) | 0.7 |
| DL | 17 (68.0%) | 17 (68.0%) | 1 |
| Coronary intervention | 22 (88.0%) | 21 (84.0%) | 1 |
| Amiodarone | 20 (80.0%) | 17 (68.0%) | 0.52 |
| beta-blocker | 25 (100%) | 25 (100%) | 1 |
| ICD | 20 (80.0%) | 21 (84.0%) | 0.77 |
| NYHA>=3 | 2 (8.0%) | 3 (12.0%) | 1 |
| Indication: Sustained VT or appropriate shock | 25 (100%) | 23 (92.0%) | 0.49 |
| Transseptal approach | 3 (92.0%) | 22 (88.0%) | 1 |
| Retroaortic approach | 2 (8.0%) | 2 (8.0%) | 1 |
| Epicardial access | 2 (8.0%) | 1 (4.0%) | 1 |
| Multipolar catheter | 25 (100%) | 25 (100.0%) | 1 |
| 3D-EMS | 25 (100%) | 25 (100%) | 1 |

329 DL, Dyslipidemia; DM, diabetes mellitus; HT, hypertension; ICD, implantable cardioverter

330 defibrillator LVEF, ejection fraction; 3D-EMS, three dimensional electroanatomical mapping system

| 555 Table 2. CT-channel geomet | 333 | Table 2. | CT-channel | geomet | ry |
|--------------------------------|-----|----------|-------------------|--------|----|
|--------------------------------|-----|----------|-------------------|--------|----|

| Table 2. CT-channel geometry | Median | Mean |
|-------------------------------|------------------|-------------|
| Number of VT isthmus/Pt | 3 [2-4.3] | 3.3+/-1.5 |
| Channel WT, mm | 3.1 [2.5-3.8] | 3.1+/-0.8 |
| Edge WT, mm | 2.3 [1.7-2.9] | 2.2+/-0.7 |
| Area of total VT isthmus, mm2 | 347 [258-559] | 402+/-191 |
| Isthmus length, mm | 28.0 [23.5-33.4] | 33.9+/-38.2 |
| Isthmus width, mm | 10.4 [8.7-12.7] | 10.9+/-3.6 |

335 CT, computed tomography; MA, mitral annulus; WT, wall thickness

| Table 3. Information of VT | LAVA-group | CT-group | P-values | |
|---|----------------------|---------------|----------|--|
| Absence of VT-induction | 1 (96.0%) | 0 (0%) | 1 | |
| VT-induction with PVS or mechanical indcution or simultaneous | 22 (02 00/) | 25 (1000/) | 0.40 | |
| induction | 23 (92.0%) 23 (100%) | | 0.49 | |
| Number of observed VT/Pt | 2 [2-3.5] | 1 [1-2] | 0.02 | |
| CL of all VT, ms | 349 [295-415] | 360 [302-387] | 0.96 | |
| Patient with mapped VT | 7 (28.0%) | 5 (20.0%) | 0.74 | |
| Number of mapped VT/Pt | 0 [0-1] | 0 [0-0] | 0.48 | |
| Number of mapped VT/Pt with VT | 1 [1-2] | 9 1 [1-1.5] | 0.67 | |
| CL of mapped VT, ms | 480 [400-546] | 450 [440-480] | 0.55 | |
| | | | | |

337 Table 3. VT characteristics

339 CL, cycle length; LAVA, local abnormal ventricular activity; LBBB, left bundle branch block; RF,

340 radiofrequency; RBBB, right bundle blanch block; VT, ventricular tachycardia

341 *Mechanical termination on the VT-isthmus

342 Table 4. Procedural characteristic and acute results

| | LAVA-group | CT-group | P-values |
|--|------------------|-----------------|----------|
| Acute outcome | - | | |
| Total mapping time (registration time) | 61.5 [39.8-83.8] | 12 [9-16] | < 0.0001 |
| Termination during VT | 11/25 (44.0%) | 8/25 (32.0%) 0. | |
| Procedure time, min | 255 [230-300] | 190 [165-215] | < 0.0001 |
| Ablation time, min | 39 [22-54] | 30 [23-45] | |
| Complication | 1 (4.0%) | 1 (4.0%) | 0 1 |
| LAVA elimination achievement | | | < 0.0001 |
| Complete LAVA elimination | 20 (80.0.0%) | 5 (20.0%) | |
| Residual LAVA (+) or Not-checked | 5 (20.0%) | 20 (80.0%) | |
| Not-checked | 0 (0%) | 5 (20.0%) | |
| VT inducibility | | | |
| VT induction performed | 21 (80.0%) | 22 (88.0%) | 1 |
| Negative VT induction | 17/21 (81.0%) | 20/22 (90.9%) | 0.41 |

345 Figure legends



Figure 1: Endpoint of LAVA guided ablation and CT-channel guided ablation

Figure 2: Follow-up

1 Yr follow up

| Follow-up | LAVA-group | CT-group | P-values |
|--------------------------|------------------------|------------------------------|----------|
| VT-recurrence at 6 month | 4 (84.0%) | 5 (80.0%) | 1 |
| VT-recurrence at 1yr | 5 (80.0%) | 6 (76.0%) | 1 |
| | CT-channel a P=0.62 | blation 600 700 (days) | |
| | | | |
| | | 99 | |

etdential intended

7. Summary and perspective

Throughout the thesis, I have described the current developments in mapping techniques and modalities. I have especially focused on the impact of high-resolution/high-density mapping systems, novel multipolar catheters, and image information for clinical use.

2020 In chapter 4, using an infarcted animal model, it is demonstrated that EGMs are strongly influenced by interelectrode 2021 spacing, activation orientation, and electrode sizes. Therefore, these factors should significantly affect the substrate 2022 distributions. The substrate of interest may be changed by these elements. If the inter-electrode spacing is too small, 2023 then bipolar electrodes may miss the intramural substrate, which may be away from the catheter. If the inter-electrode 2024 spacing is too large, then bipolar electrodes may miss the subendocardial substrates because of a far-field effect. The 2025 relationship between the activation front and the bipolar orientation may mask or unmask the substrates. Because it 2026 becomes more difficult to manually validate and annotate all EGMs in the era of high-density mapping, new 2027 technology to automatically select the correct point out of multiple points may be required to reduce unnecessary 2028 acquisition time and data volume.

2029 In chapter 5, the impact of using a novel 3D EAM system, RhythmiaTM, is demonstrated. With this new mapping 2030 tool, which generally has higher density and higher resolution compared to conventional mapping systems, the AT 2031 mechanism and accurate circuit of the tachycardia can be displayed more easily and clearly. Very few studies 2032 discussing the mechanism of scar-related ATs have been published in the past 5 years. We have not been able to 2033 observe the mechanism of scar-related ATs in detail because of the lower resolution of the mapping system and 2034 catheters. We expect to clarify the impact of using this high-resolution mapping system on the clinical outcomes. 2035 However, for better outcomes of AT ablation, not only a mapping system but also catheter technology to create 2036 durable and transmural lesions should be discussed, which is not examined in this thesis. Even if the mechanism and 2037 circuit of ATs are correctly diagnosed with the high-resolution mapping system, the clinical outcomes may not be 2038 improved if the catheter technology is not optimal. Lesions may be influenced by multiple factors such as electrode 2039 size, contact direction, contact force, RF duration, RF power, stability, and tissue characteristics. Recent catheters have a formula to unite these parameters and objectively assess the lesion^{104–107}. The impact of this technology should 2040 be elucidated. New power sources^{108–111} may dramatically change ablation outcomes, which may overcome the 2041 2042 effects of mapping technology.

2043 In chapter 6, the relationship between wall thickness distribution on CT imaging and substrate mapping using the 3D 2044 EAM for ICM patients was described. It was also demonstrated that CT channel ablation may provide similar safety 2045 and outcomes compared to LAVA ablation. The use of preprocedural imaging has several advantages, and image 2046 information registered on the 3D EAM may strongly support the ablation procedure, especially in VT. Peri-procedural 2047 3D rotational angiography could also be helpful for improving the merging of images. A novel wideband LGE-MRI 2048 technique seems promising for device artifact removal in ICD patients, with its efficacy depending on the distance 2049 from the device to the LV¹¹². Late iodine-enhanced multidetector CT has the potential to improve scar imaging in 2050 ischemic VT patients with ICDs in whom LGE-MRI is still considered strongly contraindicated^{113,114}. Learning using 2051 artificial intelligence may result in the automatic detection of potential VT isthmuses. Finally, prospective studies 2052 including randomized groups should be performed to demonstrate the superiority of guided imaging ablation and to 2053 possibly show a prognostic benefit conferred by using these imaging modalities.

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