

Leads to improve atrial fibrillation ablation, catheters, imaging and mapping guidance

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LEADS TO IMPROVE ATRIAL FIBRILLATION ABLATION, CATHETERS, IMAGING AND MAPPING GUIDANCE

Nora AL JEFAIRI, MD

Soutenue le 04/12/2017

JURY

Professor **Pierre JAIS**, Directeur de Thèse Professor **Philippe MAURY**, Rapporteur Professor **Paul-Ursmar MILLIEZ**, Rapporteur Professor **LOUIS LABROUSSE**, Examinateur

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- I. Circular catheter (nMARQ) in paroxysmal atrial fibrillation compared to point-by-point ablation
- II. Circular catheter (nMARQ) in persistent atrial fibrillation and non-invasive mapping
- III. Atrial scar on cardiac magnetic resonance and pulmonary vein reconnection

DICUSSIONS AND FUTURE PRESPECTIVES

LIST OF ABBREVIATIONS

AF	atrial fibrillation
PAF	paroxysmal atrial fibrillation
PSAF	persistent atrial fibrillation
AFL	atypical atrial flutter
AT	atrial tachycardia
SR	sinus rhythm
PV	pulmonary vein
PVI	pulmonary vein isolation
LSPV	left superior pulmonary vein
LIPV	left inferior pulmonary vein
RSPV	right superior pulmonary vein
RIPV	right inferior pulmonary vein
AADs	antiarrhythmic drugs
LA	left atrium
LAA	Left atrial appendage
EAM	electro-anatomic mapping
CL	cycle length
RF	radiofrequency
CTI	cavotricuspid isthmus

WACA	wide area circumferential ablation
CFAE	complex fractionated atrial electrograms
BDB	bidirectional block
EPS	electrophysiology study
СТ	computed tomography
MRI	magnetic resonance imaging
CMR	cardiac magnetic resonance
DEMRI	delayed enhancement magnetic resonance imaging
DEMRI LGE	delayed enhancement magnetic resonance imaging late gadolinium enhancement
DEMRI LGE TIA	delayed enhancement magnetic resonance imaging late gadolinium enhancement transient ischemic attack
DEMRI LGE TIA AEF	delayed enhancement magnetic resonance imaging late gadolinium enhancement transient ischemic attack atrio-oesophageal fistula
DEMRI LGE TIA AEF PNI	delayed enhancement magnetic resonance imaging late gadolinium enhancement transient ischemic attack atrio-oesophageal fistula phrenic nerve injury
DEMRI LGE TIA AEF PNI PNP	delayed enhancement magnetic resonance imaging late gadolinium enhancement transient ischemic attack atrio-oesophageal fistula phrenic nerve injury phrenic nerve palsy

LIST OF SCINTIFIC PUBLICATION

Submitted/under submission:

1. Relationship between atrial scar on cardiac magnetic resonance and pulmonary vein reconnection after catheter ablation for paroxysmal atrial fibrillation.

Nora Al Jefairi, MD, Claudia Camaioni, MD, Soumaya Sridi, MD, Ghassen Chniti, MD, Masateru Takigawa, MD, Hubert Nivet, MD, Arnaud Denis, MD, Nicolas Derval, MD, Francois Laurent, MD, Michel Montaudon, MD, PhD, Frederic Sacher, MD, PhD, Mélèze Hocini, MD, Michel Haissaguerre, MD, Pierre Jais, MD, Hubert Cochet, MD, PhD.

Submitted to Circulation

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2. A randomized comparison of circular versus single point-by-point pulmonary vein isolation.

Nora Al Jefairi, MD, Ruairidh Martin, MD, Antonio Frontera, MD, Arnoud Denis, MD, Nicolas Derval, MD, Frédéric Sacher, MD, Saagar Mahida, MD, Stephan Zellerhoff, Xavier Pillois, PhD, Mélèze Hocini, MD, Michel Haissaguerre MD, Pierre Jais MD. Submitted to American Journal of Cardiovascular and Thoracic Surgery

Persistent atrial fibrillation ablation using a circular irrigated ablation catheter.
Nora Al-Jefairi, MD, Ruairidh Martin⁷ MD, Jean-Marc Sellal, MD, Arnaud Denis, MD, Nicolas Derval, MD, Frédéric Sacher, MD, Saagar Mahida, MD, Stephan Zellerhoff, MD, Xavier Pillois, PhD, Mélèze Hocini, MD, Michel Haïssaguerre, MD, Pierre Jaïs, MD.
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1. Re-visiting anatomical macroreentrant tachycardia after atrial fibrillation ablation using ultra-high-resolution mapping: implications for ablation.

Takigawa M, Derval N, Frontera A, Martin R, Yamashita S, Cheniti G, Vlachos K, Thompson N, Kitamura T, Wolf M, Massoullie G, Martin C, Al-Jefairi N, Amraoui S, Duchateau J, Klotz N, Pambrun T, Denis A, Sacher F, Cochet H, Meleze H, Haissaguierre M, Jais P. Heart Rhythm. 2017 Oct 25. pii: S1547-5271(17)31243-2. doi: 10.1016/j.hrthm.2017.10.029. [Epub ahead of print]

PMID:29081399

2. Electrogram signature of specific activation patters: analysis of atrial tachycardia at high density endocardial mapping.

Frontera A, Takigawa M, Martin R, Thompson N, Cheniti G, Massoullié G, Duchateau J, Wielandts JY, Teijeira E, Kitamura T, Wolf M, Al-Jefairi N, Vlachos K, Yamashita S, Amraoui S, Denis A, Hocini M, Cochet H, Sacher F, Jaïs P, Haïssaguerre M, Derval N. Heart Rhythm. 2017 Aug 8. pii: S1547-5271(17)30962-1. doi: 10.1016/j.hrthm.2017.08.001. [Epub ahead of print] PMID:28797676

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Education is the passport to the future, for tomorrow belongs to those who prepare for it today.

Malcolm X

Résumé

La fibrillation auriculaire (FA) est la forme la plus fréquente d'arythmie cardiaque chez l'Homme. L'isolation des veines pulmonaires (VP) par radiofréquence (RF) est le traitement de référence pour les patients atteints de fibrillation auriculaire paroxystique (FAP) symptomatique réfractaire au traitement médicamenteux. L'isolation des VP fonctionne très bien pour traiter les FA paroxystiques mais elle a un rôle plus limité dans le traitement des patients atteints de FA persistante (FAPs). La FA persistante est en effet plus complexe, en raison du développement dans l'oreillette gauche (OG) d'un substrat arythmogène résultant d'un remodelage électrique et anatomique. Ce substrat maintient la FA et nécessite souvent des ablations supplémentaires dans l'OG (en dehors des veines pulmonaires).

Les récidives de fibrillation auriculaire sont principalement dues à la reconnexion électrique des veines pulmonaires. C'est un phénomène fréquent, qui limite le succès de la procédure à long terme. Certaines séries rapportent de 20 à 50% de récidive, avec un impact important pour le patient, et pour le système de santé puisque générant des hospitalisations et des procédures répétées.

L'ablation point-par-point utilisant un cathéter d'ablation à électrode unique peut être techniquement complexe. De ce fait, les lésions transmurales, contiguës et pérennes sont parfois difficiles et longues à réaliser, expliquant pour une part les taux élevés de reconnexion. Par conséquent, de nouveaux types de cathéters d'ablation ont été développés. On citera par exemple les cathéters ballons de cryoablation, les cathéters d'ablation circulaire à électrodes multiples (PVAC et nMARQ) qui sont maintenant disponibles et ont pour but la création de lésions complètes et continues. Cependant, le ballon de cryoablation a des limites, notamment dans sa capacité à s'adapter à la variabilité anatomique des VP et pour l'ablation des sites extra-veineux. La conséquence est qu'un cathéter d'ablation supplémentaire doit être utilisé pour l'ablation des sites extra-veineux ce qui rend la procédure plus complexe et coûteuse. L'absence d'irrigation du cathéter PVAC augmente sans doute le risque de complications thromboemboliques. Le cathéter nMARQ en revanche est un cathéter circulaire irrigué qui, en plus de son rôle dans l'isolation des VP, permet l'ablation de substrat en dehors des veines pulmonaires.

Par ailleurs, les outils de cartographie et d'imagerie cardiaque sont de plus en plus couramment utilisés pour planifier et guider l'ablation de FA. On citera la cartographie électro–anatomique invasive (Carto® 3, NavX, Rhythmia) et non invasive (ECVUETM), la tomodensitométrie (TDM) et l'imagerie par résonance magnétique (IRM).

Nous avons émis l'hypothèse que différentes stratégies et technologies pourraient améliorer la procédure et les résultats de l'isolation des VP en produisant de meilleures lésions et en permettant une visualisation directe des lésions. Nous avons donc évalué le rôle du cathéter circulaire irriguée pour la cartographie et l'ablation (nMARQ) dans la FAP et la FAPs avec ou sans guidage non invasif par ECGi. Nous nous sommes également intéressés à l'analyse en IRM des lésions produites par ce cathéter lors de l'isolation des veines pulmonaires. À cette fin, les données de l'isolation des VP ont été obtenues et traitées de manière aiguë et à 3 mois. Le suivi clinique a été évalué à 1 an.

La thèse se compose de 3 parties :

Partie 1: Comment améliorer l'isolation des veines pulmonaires chez les patients atteints de fibrillation auriculaire paroxystique ? Défi actuel et intérêt de l'étude : l'isolation des veines pulmonaires faite en routine est réalisée avec un cathéter d'ablation à électrode unique. L'encerclement de chaque veine pulmonaire avec des lésions punctiformes jointives est complexe et prend du temps. Des innovations technologiques ont permis de mettre au point des cryoballon (délivrant une cryocongélation) et le PVAC (délivrant un courant de RF phasée). Compte tenu des limites évoquées précédemment, nous avons voulu investiguer le rôle d'un cathéter d'ablation irrigué circulaire composé de 10 électrodes. Des études évaluant l'innocuité et l'efficacité de ce cathéter nMARQ ont été publiées, mais des essais randomisés ont été recommandés et d'autres recherches sont nécessaires pour clarifier les résultats à long terme. Une des questions importantes est notamment y a-t-il une supériorité lorsque l'isolation des veines pulmonaires est réalisée avec un cathéter multielectrode versus point–par–point. Le taux de reconnexion électrique aigu et à 3 mois est-il diffèrent ? **Hypothèse :** nous avons donc comparé dans le cadre d'une étude randomisée, le cathéter d'ablation circulaire (nMARQ) au cathéter d'ablation conventionnel (Navistar Thermocool), pour l'isolation des veines pulmonaires dans la FAP, en termes d'efficacité et de sécurité. Nous avons notamment comparé le taux de reconnexion électriques entre les deux approches, en aigu (procédure d'ablation initiale) et à moyen terme (nouvelle étude systématique à 3 mois). Puis nous avons comparé les résultats cliniques à long terme (taux de récurrence à 1 an).

Résultats : nous avons démontré, lors de la procédure initiale, qu'en comparaison de la méthode conventionnelle d'ablation, le cathéter nMARQ est 3 fois plus rapide pour l'isolation des veines pulmonaires, avec un temps de RF plus court, une durée de procédure et une exposition aux rayons X moins élevée. De plus, l'ablation des sites en dehors des veines pulmonaires (réalisée à la discrétion de l'opérateur, si l'arythmie le nécessitait) était plus rapide avec le nMARQ. Le taux de reconnexion des VP à 3 mois a été moindre dans le groupe nMARQ. La déconnexion de la veine pulmonaire inférieure droite (VPID), généralement la veine la plus difficile à isoler, était plus efficace avec le nMARQ, aussi bien lors de la procédure initiale que lors de la reprise. La durée de procédure, lors de la ré-intervention, était plus courte chez les patients qui avaient eu une procédure initiale avec le cathéter nMARQ, suggérant une reconnexion plus limitée des VP. Le cathéter circulaire n'a pas créé de complication majeure dans cette étude.

Partie 2 : Cathéter circulaire multi-électrodes et ablation de fibrillation auriculaire persistante.

Défi actuel et intérêt de l'étude : l'ablation de FAPs reste difficile et longue malgré les différentes techniques et stratégies d'ablation actuellement disponible. Si l'isolation des veines pulmonaires reste la pierre angulaire, son efficacité est plus limitée dans le traitement des FAPs, en raison sans doute du rôle du substrat atrial extra-veineux. Une nouvelle technologie d'analyse de FA utilisant une cartographie non invasive (ECVUE[™], Cardioinsight Technologies) est disponible pour identifier les sources d'arythmie (drivers) perpétuant la FA.

Hypothèse : le but de l'étude était d'analyser, dans le contexte de la FAPs, l'intérêt du cathéter circulaire (nMARQ) pour l'isolation des veines pulmonaires et surtout les lésions créées en dehors des veines pulmonaires (ablation des potentiels fractionnés, ablation des zones de rotors, lésions linéaires des isthmes cavotricuspide, mitral et du toit. Les applications de radiofréquence étaient guidées par système cartographique 3D (Carto® 3, Biosense), avec ou sans cartographie non invasive (ECVUE[™], Cardioinsight). Nous avons évalué les résultats cliniques à long terme et notamment le taux de récurrence à 1 an.

Résultats : l'étude montre une efficacité et une sécurité satisfaisantes en utilisant nMARQ dans l'ablation de FAPs. En plus de l'isolation des veines pulmonaires, ce cathéter d'ablation se montre polyvalent, permettant de traiter des sites de potentiels fractionnés ou des rotors en

dehors des veines pulmonaires. Il permet également dans un nombre non négligeable de cas de bloquer les isthmes cavotricuspide, mitral, et du toit. La combinaison de nMARQ avec une cartographie ECGi non invasif était particulièrement rapide et efficace.

Partie 3 : Rôle de l'imagerie par résonance magnétique dans l'évaluation de la reconnexion des veines pulmonaires après l'isolement des veines pulmonaires ?

Défi actuel et intérêt de l'étude : La reconnexion des veines pulmonaires après l'ablation de FA est très fréquente. Des études portant sur l'état des VP chez les patients en récidive de FA ont démontrées un taux important de reconnexion des VP et le besoin de ré-ablation (chez 20 à 50% des patients) pour finalement réussir à maitriser l'arythmie. L'impact sur la qualité de vie et le fardeau économique pour les systèmes de santé est substantiel. L'IRM s'améliore constamment, avec un meilleur matériel et de meilleures séquences d'imagerie permettant une détection et une quantification plus précises notamment des lésions de RF.

Hypothèse : l'objectif primaire de l'étude était d'utiliser une séquence de rehaussement tardif en IRM (RTIRM) pour caractériser la cicatrice (lésions de RF) après l'isolation des veines pulmonaires, et pour comprendre si l'IRM pourrait déterminer de manière non invasive, si les VP sont isolés ou non. À cette fin, nous avons effectué à la fois l'IRM et une étude électrophysiologique systématique de l'OG et des VP à 3 mois, indépendamment de la récidive de FA. Nous avons émis l'hypothèse que l'IRM pourrait jouer un rôle dans la prédiction, la caractérisation et

la localisation de la reconnexion des VP. L'objectif secondaire était de comparer les lésions de RF après l'isolation des veines pulmonaires entre le cathéter à électrode unique et le cathéter circulaire multi-électrodes.

Résultats : notre étude a confirmé que la reconnexion des PV était extrêmement fréquente après l'isolation des veines pulmonaires. Nous avons constaté que la quantification des lésions de RF à l'IRM prédisait avec précision le résultat clinique. Lorsqu'un gap dans la lésion d'isolation était visible à l'IRM, il était confirmé par cartographie. En revanche, certains gaps visibles en cartographie n'étaient pas visibles en IRM, certainement du fait d'une résolution spatiale encore trop faible. En outre, nous avons constaté que le cathéter d'ablation circulaire multi–électrode crée des lésions plus complètes par rapport au cathéter d'électrode unique à ablation conventionnel.

Thesis Summary

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in Humans. Pulmonary vein isolation (PVI) by radiofrequency (RF) ablation is the mainstay treatment for patients with symptomatic and drug refractory paroxysmal atrial fibrillation (PAF) as ectopic beats (triggers) from pulmonary veins (PVs) initiate AF, however PVI alone had limited role in treating patients with persistent atrial fibrillation (PAF), due to additional involvement in left atrium (LA) by electrical and anatomical remodeling, creating more complex substrate (fibrosis) that maintain AF and therefore necessitate non-PV sites ablation to modify the arrhythmogenic substrate.

Atrial fibrillation recurrence mainly due to pulmonary vein (PV) electrical reconnection is common and remains the current issue that limits long term procedural success and generates extra costs due to repeated hospital admissions and repeated procedures.

Point-by-point catheter ablation using single tip catheter can be challenging, complex and time consuming, enhancing electrical reconnection as stable lesions are difficult to achieve. To overcome these limitations, new type of catheters such as balloon (cryoablation) and multi-electrode circular ablation catheters like PVAC and nMARQ, are now available. However, cryoablation balloon is limited by inability to adapt to anatomic PV variability and to ablate non-PV sites. This means that an additional ablation catheter has to be used for non-PV

targets, and it certainly adds to the costs. The PVAC catheter lacks of irrigation increases the risk of thromboembolic complications. On contrary, nMARQ is an irrigated circular ablation catheter which in addition to its role in PVI, allows for non-PV/LA substrate ablation.

Cardiac mapping and imaging tools are now commonly used to plan and guide AF ablation, such as invasive (Carto® 3) and noninvasive (ECVUETM) electro–anatomic mapping (EAM), computed tomography (CT) and magnetic resonance imaging (MRI), respectively.

We hypothesized that different strategies and technologies could improve PVI procedure and outcome by producing better lesions and by allowing for direct visualization of lesions. We therefore, assessed the role of circular, irrigated mapping and ablation catheter (nMARQ) in PAF and PsAF with or without noninvasive ECGi guidance, and advanced imaging technologies (MRI) after PVI. For that purpose, PVI data were obtained and processed acutely and at 3 months. Clinical follow up was evaluated at 1 year.

The thesis consists of 3 parts:

Part 1: How to improve PVI lesion formation in patients with PAF?

Current challenge and rationalism: point–by–point standard PVI using single tip ablation catheter can be complex and time consuming. Balloon and circular catheters are now available, such as PVAC (delivering phased RF) and cryoballoon (delivering cryo/freezing), respectively, but carry limitations in AF ablation as previously explained. The circular irrigated mapping and ablation catheter was developed to overcome some of these limitations. Studies were available to evaluate nMARQ safety and efficacy, however, further randomized trials were recommended and further research was needed to clarify long term outcome. In addition, a direct randomized comparison versus the conventional point by point ablation has not been conducted.

Hypothesis: we aimed to compare circular ablation catheter (nMARQ) to conventional point by point single catheter (Navistar Thermocool), for PVI in PAF, in term of efficacy and safety. The comparison included acute (index) and late (after 3 months of repeated procedure) electrical evaluation of reconnection rate between both approaches, with long term clinical outcome evaluation.

Results: we demonstrated that the nMARQ catheter is 3 times faster for PVI with shorter RF time, procedure time and lesser x-ray exposure when compared to conventional procedure in index procedure. Non-PV sites ablation (when needed) was faster with nMARQ in index procedure. PV reconnection at 3 months was fewer with nMARQ. Right inferior pulmonary vein (RIPV) 'the challenging vein to isolate' ablation was more effective (less reconnection) with nMARQ, both in index and repeated procedure. Repeated procedure time was shorter in patients who had index procedure with nMARQ catheter suggesting fewer/milder PV reconnection. The circular catheter seemed to be safe with no major procedural complications.

Part 2: Circular catheter and PsAF ablation

Current challenge and rationalism: catheter ablation for PsAF remains challenging and time consuming despite different ablation techniques and strategies. PVI remains the corner stone here as well, but with a more limited efficacy because of additional involvement of LA substrate (fibrosis). This is why it is usually combined with additional ablation. New technology of AF analysis using noninvasive body surface mapping (ECVUE, Cardioinsight Technologies) has become available to identify focal or reentry/rotors that play a role in driving and maintain AF.

Hypothesis: the aim of the study was to investigate the role of circular catheter (nMARQ) in PsAF in PVI and especially non-PV ablation/linear lesions (cavotricuspid isthmus, mitral isthmus and roof line). Procedures were guided by 3D Carto (Complex fractionated atrial electrograms (CFAE) based ablation) with or without noninvasive mapping ECVUE Cardioinsight (driver based ablation) and 1 year clinical outcome evaluation reported.

Results: the study reports efficacy and safety using nMARQ in PsAF ablation. It demonstrates the versatility of this ablation catheter which could be used to successfully ablate the cavotricuspid isthmus (CTI), non-PV sites, as well as mitral isthmus and roof, in addition to PVI, therefore, obviating the need for an additional ablation catheter in a majority of patients. The combination of nMARQ with non-invasive ECGi mapping was particularly fast and effective.

Part 3: The role for MRI in assessing PV reconnection after PVI?

Current challenge and rationalism: pulmonary vein reconnection after AF ablation is very commonly observed. Studies investigating the status of PVs in patients with AF recurrences demonstrated a very high rate of PV reconnection and the need for PV re-ablation (in 20 to 50% of patients) to finally achieve a successful outcome. The impact on quality of life and economic burden for health care systems is very significant. MRI is continuously improving, with better hardware and better imaging sequences allowing for more accurate RF lesion detection and quantification.

Hypothesis: the aim of the study was to use delayed enhancement magnetic resonance imaging (DEMRI) to characterize RF lesions after PVI and to understand if MRI could determine non-invasively if PVs are isolated or not. For that purpose, we performed both MRI and systematic electrophysiological re-study of the LA and PVs at 3 months regardless of AF recurrence. We hypothesized that MRI may have a role in predicting, characterizing and localizing PV reconnection. A secondary objective was to compare the RF lesions and PV electrical reconnection after PVI between single–electrode and circular multi–electrode ablation catheters.

Results: our study confirmed that PV reconnection is extremely frequent after PVI for PAF. We found that the amount of RF lesions at DEMRI was accurately predicting the clinical outcome. When a gap in PVI lesions was visible at MRI, it was confirmed by mapping, but the spatial

resolution seems too low for accurately identifying all of them. In addition, we found that multi–electrode circular ablation catheter creates

more complete lesions compared to the conventional single ablation electrode catheter.

Chapter 1

INTRODUCTION

Atrial Fibrillation and Catheter Ablation

Catheter Ablation Technologies and Challenges

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common supraventricular arrhythmia (> 30 seconds) characterized by complex spatiotemporal organization and non-uniform conduction, found particularly in the elderly or in whom with a known heart disease (figure 1). Despite the progress in the management of symptomatic patients with atrial fibrillation, this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular comorbidity in the world[1]. AF is a real public health problem which puts significant pressures on the domestic health service and therefore causes a major socio-economic cost, ultimately emphasizing the need for research into better diagnostic, management and treatment of AF.



Figure 1: Normal sinus rhythm (left) versus atrial fibrillation (right) electrical activation[2].

Epidemiology, impact for patients and health care burden

In 2010, the estimated numbers of men and women with AF worldwide were 21 million and 13 million, respectively, with higher incidence and prevalence rates in developed countries[3, 4]. One in four middle-aged adults in Europe and the US will develop AF[5-7]. The incidence of AF increases strongly with age: < 1/1000 per year before 40 years, 5/1000 per year around 60 years and > 15-20/1000 per year after 80 years. By 2030, 14-17 million AF patients are anticipated in the European Union, with 120 000-225 000 newly diagnosed patients per year [4, 8, 9]. Estimates suggest an AF prevalence of approximately 3% in adults aged 20 years or older[10, 11], with greater prevalence in older persons[3] and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus (DM), or chronic kidney disease (CKD)[9, 12-17]. In France, between 600 000 and 1 million people are estimated to have AF[18]. The increase in AF prevalence can be attributed both to better diagnostic techniques of silent AF[19-21], alongside increasing age and conditions predisposing to AF[19-22].

AF is independently associated with a two-fold increase risk of all-cause mortality in woman and a 1.5-fold increase in men[23-25]. Death due to stroke can largely be mitigated by anticoagulation, while cardiovascular deaths due to heart failure and sudden death remain common even in AF patients treated according to the current evidence base[26]. AF is also associated with increased morbidity; such as heart failure, stroke and cognitive impairment [24, 27-29], decreased quality of life[30] and 10-40% hospitalization each year [26, 31, 32].

The direct costs of AF already mount to approximately 1% of total healthcare spending in the UK, and between 6–26 billion US dollars in the US for 2008[33, 34], driven by AF-related complications (e.g. stroke) and treatment costs (e.g. hospitalizations). Half a million patients with AF were hospitalized in France in 2012[35]. Cardiovascular-related hospitalization involved half of these admissions, for a global burden of almost ϵ_2 billion of which heart failure represented ϵ_{805} million, vascular/ischemic disease ϵ_{386} million, stroke ϵ_{362} million, cardiac dysrhythmia ϵ_{341} million, and hemorrhage ϵ_{48} million, equivalent to 2.6% of total expenditure in France hospitals[35]. Among these hospitalizations stroke/transient ischemic attack (TIA)/ systemic embolism (SE) represented costly, but preventable, complications[35]. These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner and hence the importance of further research to further elucidate effective ablation techniques and evaluate the role of advanced imaging technologies for treating AF.

Pathophysiological and genetic aspects

Genetic Predisposition

AF, especially early-onset AF, has a strong heritable component that is independent of concomitant cardiovascular conditions[36, 37]. Up to one-third of AF patients carry common genetic variants that predispose individuals to AF with a relatively low added risk. At least 14 of these variants, often single nucleotide polymorphisms are known to increase the risk of prevalent AF in population[38-40]. The most important variants are located close to the paired-like homeodomain[41, 42] including the transcription factor 2 (Pitx2) gene on chromosome 4q25.

Several AF risk variants are also associated with cardio-embolic or ischemic stroke, possibly due to silent AF[40, 43, 44]. Changes in atrial action potential characteristics[45-48], atrial remodeling, and modified penetration of rare gene defects[39] have been suggested as potential mechanisms mediating increased AF risk in carriers of common gene variants. Genetic variants could, in the future, become useful for patient screening and selection of rhythm or rate control[49-52]. At present, routine genetic testing for common gene variants associated with AF are not recommended[53].

Mechanisms leading to atrial fibrillation

1. Remodelling of atrial structure and ion channel function

Clinical conditions such as structural heart disease, hypertension, diabetes and AF itself induce a slow but progressive process of structural remodeling in the atria[1], by activation of fibroblasts that enhance connective tissue deposition, and fibrosis[54-56], in addition to atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis and amyloidosis [57-60]. The pathophysiological alteration results in enhancing the pro-arrhythmic mechanism and functional consequences, by electrical dissociation[61], favoring re-entry and perpetuation of the arrhythmia[62] and ultimately predisposing a prothrombotic state, especially in the left atrial appendage (LAA) increasing stroke risk [63, 64] (figure 2). This auto-reinforcing property of AF burden enhances the vulnerability of atrial tissue to AF induction (propensity to ectopy), maintenance (fibrosis) and transformations or progression (substrate modification/ structural and electrical remodeling) from

intermittent, self-converting AF episodes (paroxysmal) to continuous, long lasting, needing cardioversion (persistent or permanent), often referred to by the term (AF begets AF) (figure 3). As some of the structural remodeling will be irreversible, early initiation of treatment seems desirable[65].



AnglI = angiotensin II; TF = tissue factor; FXII = factor XII; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor I; VCAM-1 = vascular cell adhesion molecule 1.

Figure 2: The diagram illustrates Atrial fibrillation mechanisms. Etiological factors (left) cause pathophysiological changes in the atria, including stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodeling, ischemia, ion channel dysfunction, and Ca2+ instability. These changes enhance both ectopy and conduction disturbance, increasing the propensity of the atrial to develop or maintain AF. At the same time, some of these alterations are involved in the occurrence of the hypercoagulable state associated with AF. For example, hypocontractility reduces local endothelial shear stress, which increases PAI-1 expression, and ischemia-induced inflammation enhances the expression of endothelial adhesion molecules or promotes shedding of endothelial cells, resulting in tissue factor exposure to the blood stream. These changes contribute to the thrombogenic milieu in the atria of AF patients. AF in itself can aggravate many of the mechanisms shown, which may explain the progressive nature of the arrhythmia[1].

AF Mechanisms



Figure 3: Principal atrial fibrillation (AF)-maintaining mechanisms. A: Local ectopic firing- B Single-circuit re-entry. C: Multiple-circuit re-entry. D: Clinical AF forms and relation to mechanisms. Paroxysmal forms show a predominance of local triggers/drivers, particularly from pulmonary veins (PVs). As AF becomes more persistent and eventually permanent, re-entry substrates (initially functional and then structural) predominate. RA indicates right atrium; SVC, superior vena cava; LA, left atrium; and IVC, inferior vena cava[66].

2. Electrophysiological mechanisms

AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the arrhythmia, due to down-regulation of the Ca^{2+} inward current and up-regulation of the inward rectifier K⁺ currents in myocytes[67, 68]. Structural heart disease, in contrast, tends to prolong the atrial refractory period, illustrating the heterogeneous nature of AF mechanisms[69]. Hyperphosphorylation of Ca^{2+} handling proteins contribute to spontaneous Ca^{2+} release and trigger activity[70, 71], causing ectopy and altering autonomic tone [56, 72], generating AF (figure 4).
Ion Channel Determinants of Reentry

A Determinants of refractory period (RP) B Determinants of conduction velocity (CV)



Figure 4: Abnormalities of refractoriness (A) and conduction velocity (B) are the major determinants of atrial fibrillation (AF) re-entry substrates. Refractory period (RP) is determined by action potential duration, which is governed by the balance between inward (down-going) and outward (up-going) currents. Conduction velocity is determined by inward currents providing depolarization energy (mainly Na⁺) and gap junction channels (connexions) providing cell-to-cell electric continuity. Increased outward K⁺ currents or decreased inward Ca²⁺ currents reduce RP, promoting AF by accelerating repolarization (dashed line)[66].

Focal initiation and maintenance

The mechanism of focal activity involves both triggered activity and localized re-entry[73, 74]. The focal source is observed in the pulmonary veins triggering AF, therefore, ablation of this source can suppress AF[75].

The multiple wavelet hypothesis and rotors as sources of atrial fibrillation

AF can be perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a chaotic manner capable of sustaining the arrhythmia[76]. All localized sources of AF (ectopic foci, rotors, or re-entry circuits) cause fibrillatory conduction remote from the source, which is difficult to distinguish from propagation to sustain AF by multiple wavelets, and either of these phenomena my generate 'rotor' picked up by intra-cardiac[77, 78] or body surface[78] recordings (figure 5).



Figure 5: Conceptual models of re-entry and implications for atrial fibrillation (AF). A: Leading circle. B: Spiral-wave reentry. C: In normal atria, the number of reentrant waves that can be accommodated is small, and reentry easily terminates. D: When wavelength (WL) is reduced, by decreasing the refractory period (RP) or conduction velocity (CV), reentrant circuit are smaller and more can be accommodated; AF becomes unlikely to self-terminate. E: Drugs that increase wave reduce the number of circuits, favoring AF termination[66].

3. Pulmonary veins as a source of triggering and maintaining atrial fibrillation

Pulmonary veins (PVs) initiate up to 94% of AF[75]. Ectopic beats (triggers) from PV interact with atrial substrate (striated myocardial sleeves) by electrical connection to the LA (figure 6); therefore, ablation at these connections electrically isolates the PVs[79-82]. However, even after electrical isolation, up to 33% of PVs have spontaneous or induced tachycardia within the PV, highlighting their arrhythmogenic potential[83-85]. In some cases, PVs formed are not only the trigger but also the substrate responsible for maintaining AF (focally driven AF)[86]. PVI in paroxysmal AF (PAF) culminating in the termination of AF in 75% of patients and rendered AF noninducible in 57%, providing evidence that PVs or PV-LA junction formed the perpetuators and substrate of AF[87, 88]. PV dilatation in patients with AF is a marker of structural changes within the PVs (discontinuous myocardium, hypertrophic myocytes, and fibrosis) that are promoting PV arrhythmogenesis[89-92].



Figure 6: Cross-sectional intravascular ultrasound (IVUS) images and histological cross-sections evaluating pulmonary venous wall at the veno-atrial junction (panel A and B) and showing PV muscle sleeves (white and red arrows) that often covering less that the full circumference of the vein (panel C and D) [93].



Figure 7: Summary of the electrophysiologic substrate in posterior LA wall amenable to catheter ablation. Several mechanisms may coexist in the same patient. IVC = inferior vena cava, LI = left inferior, LOM = ligament of Marshall, LS = left superior, PV = pulmonary vein, RV = right inferior, RS = right superior, SVC superior vena cava[94].

Clinical presentation

Atrial fibrillation has a wide spectrum of clinical presentation. While some patients may be asymptomatic, others may present with stroke, heart failure, or cardiac arrest[95]. Patients most commonly report palpitations, dyspnea, fatigue, light-headedness, and chest pain. As symptoms are nonspecific, they cannot be used to diagnose and determine the onset of AF[96].

Diagnosis

The diagnosis of AF requires rhythm documentation using an electrocardiogram (ECG) (figure 8) showing the typical pattern of AF: absolutely irregular RR intervals and no discernible, distinct P waves. ECG documented AF was the entry criterion in trials forming the evidence for the European Society of Cardiology (ESC) guidelines[1], by accepted convention, an episode lasting at least 30 seconds is diagnostic. Individuals with AF may be symptomatic, asymptomatic (silent AF) or have both[97-100]. Silent, undetected AF is common [99, 101], therefore, prolonged ECG monitoring enhances the detection of undiagnosed AF, e.g. monitoring for 72h after a stroke [21, 102, 103], or even longer periods [21, 104]. Once the ECG diagnosis of AF is established further ECG monitoring can inform management in the context of: (1) a change in symptoms or new symptoms; (2) suspected progression of AF; (3) monitoring of drug effects on ventricular rate; and (4) monitoring of antiarrhythmic drug (AAD) effects or catheter ablation for rhythm control[1].





Figure 8: 12-lead ECG showing irregularly irregular rhythm of AF.

Classification of atrial fibrillation[1]

In many patients, AF progresses from short, infrequent episodes to longer and more frequent episodes. Over time, many patients develop sustained forms of AF. AF may also regress from persistent to paroxysmal.

Based on the presentation, duration, and spontaneous termination of AF episodes, five classes can be distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (table 1). AF episodes may be detected at the first time, paroxysmal; when they terminate spontaneously, usually within seven days, or persistent; when the arrhythmia continues requiring electrical or pharmacological cardioversion for termination. AF that cannot be successfully terminated by cardioversion is termed longstanding (> 1 year) and when cardioversion is not indicated or has not been attempted, it is termed permanent. The different classification of AF helps in choosing the appropriate therapeutic approach pharmacologically and the ablation strategy accordingly.

AF is a major contributor to increased mortality rates [23] and an independent risk factor predisposing to stroke[105, 106]. Although paroxysmal AF episodes lasting less than 30 seconds have traditionally been considered of little prognostic importance, a study showed that even high atrial rates of short duration are associated with higher risk for acute and chronic strokes [107, 108]. The prognosis of patient with AF is worse in certain at-risk subgroups, including those with heart failure, acute myocardial infarction, and chronic kidney disease[19, 109-

111]. The presence of AF: in heart failure was associated with a greater than 2-fold higher risk of death compared to those with heart failure alone[112], in myocardial infarction was associated with a 4-fold when compared to those with no AF[113] and in chronic kidney disease was associated with an over 50% increased risk of thromboembolism [110].

Table 1: Pattern of AF[1]

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. ^a AF episodes that are cardioverted within 7 days should be considered paroxysmal. ^a
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

AF = atrial fibrillation.

^aThe distinction between paroxysmal and persistent AF is often not made correctly without access to long-term monitoring^[114]. Hence, this classification alone is often insufficient to select specific therapies. If both persistent and paroxysmal episode are present, the predominant pattern should guide the classification.

Management

AF management comprises therapies with a prognostic impact (anticoagulation to prevent stroke and treatment of underlying cardiovascular conditions) and therapies predominantly providing symptomatic benefit (rate control, rhythm control and catheter ablation)[1].

Anticoagulation: AF increases the risk of thromboembolic events by nearly 5-fold[106]. Oral anticoagulation (OAC) with vitamin K antagonist (VKAs) or non-VKA oral anticoagulation (NOACs) markedly reduces stroke and mortality in AF patients[115-118]. Warfarin and other VKAs were the first anticoagulants used in AF patients. Their mechanism of action is prevention of the intrahepatic metabolism of vitamin K epoxides and therefore an induction of vitamin K deficiency. As a result, thrombin generation slows, and clot formation becomes impaired due to decreased biologic activity of the prothrombin complex proteins[119]. The effect of VKAs is gradual, reversible and measured by monitoring the prothrombin time (expressed as the international normalized ratio (INR)). NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, are suitable alternatives to VKAs for stroke prevention in AF[1]. Their use in clinical practice is increasing rapidly. All NOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring. The initial decision for OAC in AF patients is estimated by stroke risk based on the CHA₂DS₂-VASc score[120] (table 2). In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors

(i.e. CHA₂DS₂-VASc score of one or more for men, and 2 or more for women) are likely to benefit from OAC[1]. Anticoagulation increases risk of bleeding in an anti-coagulated patient. General clinical assessment of modifiable and non-modifiable risk factors for bleeding, and laboratory tests are recommended, such as patients with hypertension, chronic kidney disease (CKD), alcohol abuse, and concurrent medications[1]. In a meta-analysis of 47 studies, the overall incidence of major bleeding with VKAs was 2.1 (range 0.9-3.4) per 100 patientsyears in controlled trials and 2.0 (range 0.2-7.6) per 100 patient-years for observational data sets[121]. Table 2: Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc risk factor	Points	
Congestive heart failure: Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1	
Hypertension: Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1	
Age 75 years or older	+2	
Diabetes mellitus: Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycemic agent and/or insulin	+1	
Previous stroke, transient ischemic attack, or thromboembolism	+2	
Vascular disease: Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1	
Age 65–74 years	+1	
Sex category (female)	+1	

 CHA_2DS_2 -VASc score = Congestive Heart failure, hypertension, Age \geq 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)[1]

Rate control: Pharmacological rate control is achieved with beta-blockers, digoxin, calcium channel blockers (diltiazem and verapamil), or combination therapy. Amiodarone can be useful for rate control as a last resort as a reserve agent in patients whose heart rate cannot be controlled with combination therapy[1]. The optimal heart rate target in AF patients is unclear. The randomized RACE (Rate Control Efficacy in Permanent Atrial Fibrillation) study of 614 patients showed no difference in a composite of clinical events, NYHA class, or hospitalizations between target hear rate < 80 b.p.m at rest and < 110 b.p.m during moderate exercise (strict rate), or to a lenient heart rate target of < 110 b.p.m, 15% versus 13%, respectively[122, 123]. Similar results were found in a pooled analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials (1091 participants), albeit with smaller heat rate differences and without randomization[124].

Rhythm control: Cardioversion to restore normal sinus rhythm is achieved electrically or pharmacologically. Pharmacological cardioversion and maintenance of normal sinus rhythm are difficult to achieve because of the limited long-term effectiveness of medications, the risk of triggering ventricular arrhythmia, and the risk of long-term adverse effects from medication use[95]. Medications commonly used for cardioversion include amiodarone, dronedarone, flecainide, propafenone, quinidine, disopyramide, sotalol and dofetilide[1]. The choice of medication depends on the patient's cardiac history. For example, flecainide and propafenone are preferred in patients with minimal or no

heart disease and preserved left ventricular systolic function, whereas amiodarone and dofetilide are preferred in patients with heart failure[96].

Rate control versus rhythm control: Rate control and Rhythm control improve AF-related symptoms and preserve cardiac function, but have not demonstrated a reduction in long-term morbidity or mortality[117, 118]. Although antiarrhythmic drugs (AADs) have been the mainstay treatment for AF, their limited efficacy and potential for significant adverse effects have led to a renewed interest in rate control measures, stimulated by publication of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM)[125], the Rate Control versus Electrical cardioversion (RACE)[126], and the Pharmacological Intervention in Atrial Fibrillation (PIAF)[127] trials, which suggested an equivalent outcome for pharmacologic rhythm and rate control strategies (table 3). However, these findings have highlighted the fact that the benefits of sinus rhythm can be negated by the deleterious effects of antiarrhythmic drugs. A further analysis of the AFFIRM results demonstrated that sinus rhythm was associated with a 47% lower risk of death, whereas the use of antiarrhythmic drugs significantly increased mortality risk by 49% [128]. Therefore, restoration and maintenance of sinus rhythm is of potential benefit if it can be achieved without the use of antiarrhythmic drugs, and this fact underscores the need to strive for the development of non-pharmacologic treatments to achieve and maintain sinus rhythm.

Antiarrhythmic drugs are associated with a number of side effects including; arrhythmias and toxicities. For example, flecainide is associated with minimal risk of proarrhythmic in patients with structurally normal heart[129] but increase in QRS duration by 15 to 20%[130] and the chance of proarrhythmic toxicity increases with increased heart rate. Amiodarone commonly leads to QT interval prolongation but the risk of torsades de pointes is relatively minor (< 1%) due to its homogeneous blockade of the potassium channels[131] but major toxicities of amiodarone include hyper- and hypothyroidism, ophthalmic, hepatic and pulmonary side effects are present[129]. Sotalol is ineffective in terminating AF and should be avoided in patients with creatinine clearance arte of less than 40 mL/min but it can be effective in preventing arrhythmia [129, 132].

Trial	Year	Pt no	HF %	Mean Age	Rhythm	Rate	Outcomes
PIAF[127]	2000	252	4	y 60.5	Amiodarone or DCCV	Diltiazem, BB, Digoxin or AVNA + PM	No significant differences in quality of life in patients in SR or AF
AFFIRM[125]	2002	4060	23	70	Amiodarone, sotalol, propafenone, procainamide	Digoxin, BB, Diltiazem, Verapamil	No significant differences in all-cause mortality, trend toward increased mortality with rhythm control
RACE[126]	2002	522	50	68	Sotalol, flecainide, propafenone, amiodarone	Digoxin, CCB, BB	No significant differences in composite end point (cardiovascular death, CHF, embolic events, bleeding, PM, severe adverse effects of AADs)

Table 3: Major trials comparing rate versus rhythm control strategy for atrial fibrillation

DCCV= direct current cardioversion, BB = beta blockers, AVNA = atrioventricular nodal ablation, CCB = calcium channel blockers. CHF = congestive heart failure. AADs= antiarrhythmic drugs[133].

Catheter ablation versus antiarrhythmic drugs: catheter ablation is effective in restoring and maintaining sinus rhythm (SR) in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF, in general as a second-line treatment after failure of or intolerance to AAD therapy[1]. In such patients, catheter ablation is more effective than AAD therapy[134-140]. A meta-analysis of randomized controlled trials on the effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation showed that AF recurrence

was reduced in patients who underwent catheter ablation therapy[141] (figure 9). As first-line treatment for paroxysmal AF, randomized trials showed only modestly improved rhythm outcome with catheter ablation compared to AAD therapy[142-145]. A systematic review summarizing the available evidence on the role of catheter ablation as a first-line therapy for PAF demonstrated that catheter ablation is more effective than AADs for the long-term maintenance of sinus rhythm and is associated with comparable rates of adverse events in relatively young patients with minimal structural heart disease[146] (figure 10). A recent trial showed that catheter ablation improves outcomes on all-cause mortality and hospitalization rates for patients with left ventricular dysfunction and atrial fibrillation compared to state-of- the art conventional treatment recommended by the American Heart Association and the European Society of Cardiology according to late-breaking results from the CASTEL-AF trial[147]. Limited data is available reporting the effectiveness and safety of catheter ablation in patients with persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared to AAD therapy with or without cardioversion[134, 137, 145, 148-151].

	Catheter ablation		AADs		Risk Ratio		Risk Ratio	
Study	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H, Random, 95% Cl	
Krittayaphong et al.2003	3	15	9	15	3.1%	0.33 [0.11, 0.99]		
Wazni et al. 2005	4	33	22	37	3.9%	0.20 [0.08, 0.53]	· · · · · · · · · · · · · · · · · · ·	
Stabile et al. 2006	30	68	63	69	13.2%	0.48 [0.37, 0.64]	+	
Oral et al. 2006	20	77	29	69	9.3%	0.62 [0.39, 0.99]		
Jais et al. 2008	7	53	42	59	5.9%	0.19 [0.09, 0.38]		
Forleo et al. 2009	7	35	20	35	5.8%	0.35 [0.17, 0.72]		
Wilber et al. 2010	35	106	47	61	12.6%	0.43 [0.32, 0.58]		
Pappone et al. 2011	27	99	43	99	10.8%	0.63 [0.42, 0.93]		
Nielsen et al. 2012	22	146	43	148	9.5%	0.52 [0.33, 0.82]	-	
Blandino et al. 2013	37	153	141	259	12.6%	0.44 [0.33, 0.60]	-	
Morillo et al. 2014	36	66	44	61	13.3%	0.76 [0.58, 0.99]	-	
Total (95% CI)		851		912	100.0%	0.47 [0.38, 0.58]	•	
Total events	228		503					
Heterogeneity: Tau ² = 0.07	; Chi ² = 26.31,	df = 10 (P = 0.003); ² = 6	32%			
Test for overall effect: Z = 6	5.93 (P < 0.000	01)					0.05 0.2 1 5 20 Favors catheter ablation Favors drug therapy	

Figure 9: Forest plot of the effects of catheter ablation versus antiarrhythmic drugs (AADs) of the recurrence of atrial fibrillation. CI, confidence interval[141].



Figure 10: Plot showing individual and pooled success rates (left) and complication rates (right) of catheter ablation (CA) and antiarrhythmic drug (AAD) therapy in studies evaluating CA as first-line therapy for atrial fibrillation. CI, confidence interval; OR, odds ratio[146]. RAAF, Radiofrequency Ablation versus Antiarrhythmic drugs as First-line Treatment of symptomatic atrial fibrillation. MANTRA, Medical ANtiarrhthmic Treatment or Radiofrequency Ablation.

CATHTER ABLATION FOR ATRIAL FIBRILLATION

Catheter ablation by radiofrequency (RF) is a minimally invasive procedure to treat atrial fibrillation. Radiofrequency current transfers electromagnetic energy into thermal energy by a process called resistive, conductive heating at the surface of tissue. Lethal heating destroys deeper tissue by conduction[152]. The RF current is delivered in a unipolar (between the catheter tip and the indifferent electrode patch placed on skin) or bipolar (current flows between two closely apposed small electrodes) systems[152].

Ablation targeting the PVs forms the central theme in all strategies currently used for AF ablation. Other ablation strategies requiring non-PV triggers ablation and substrate modification, especially for persistent and long-standing AF, are required to control and manage AF, such as lines ablation, complex fractionated atrial electrograms (CFAEs) and rotor modulation. However, outcomes improve after repeat procedures.

A combination of tools is used to ensure electrophysiologic guidance and comfort, in addition to anatomic framework for AF ablation. Knowledge of the LA-PV anatomy provided by imaging such as, computed tomography (CT) or magnetic resonance imaging (MRI) is useful, particularly in the presence of anatomic variations. Catheter tracking systems are useful as navigation and mapping tools for nonfluoroscopic monitoring of catheter position and tagging ablation[153, 154]. Indication for catheter ablation





Figure 11: Indications for catheter ablation of symptomatic atrial fibrillation. Shown in this figure are the indications for catheter ablation of symptomatic paroxysmal, persistent, and long-standing persistent AF. The Class for each indication based on whether ablation is performed after failure of antiarrhythmic drug therapy or as first-line therapy is shown[155].

Tools used for ablation: cardiac mapping and imaging

Invasive electro-anatomic mapping

The electro-anatomic mapping (EAM) or CARTO system (Carto® 3, Biosense Webster, Baldwin Park, Calif.) has become widely used, especially in single tip (point-by-point) or circular mapping (navigation) and ablation procedures providing anatomic and electrophysiologic guidance (figure 12). Carto 3 is an accurate (+/-1 mm), ACL hybrid technology with magnetic and linear field current-based, not affected by biological changes. The system contains a metal coil placed in a magnetic field that generates an electric current. The catheter is utilized for fast anatomical mapping (FAM), single tip (Navistar Thermocool) or circular (nMARQ) contain a location sensor in the catheter tip. Three ultra-low magnetic fields are emitted from a unit mounted under the patient table. Data for amplitude, frequency, and phase of the magnetic field are gathered and analyzed by a processing unit to determine the location and the orientation of the catheter tip. A three-dimensional (3-D) real-time map is created by first placing the catheter under fluoroscopic guidance in a known anatomic position acting as landmarks. Other points in the interested chamber (left atrium LA and pulmonary veins PV) are accurately mapped for electro-anatomic chamber constriction. Computer analysis of these points is used to create a real-time, 3-D model. In addition, a local electrogram is produced at each point and gated to the preselected reference electrogram. Therefore, navigation and mapping are useful for non-fluoroscopic monitoring of catheter position and to tag regions being ablated. [153, 154]. These electrograms create a voltage, activation, or propagation color-coded

map. Specific anatomical or ablation points of interest could be tagged for reference. Multiple projections of the model (LA) can be viewed on a graphical display unit.

Integrating computed tomography (CT) or magnetic resonance imaging (MRI) with 3-D mapping (CartoMerge, Biosense Webster, Diamond Bar, CA) to guide catheter ablation of AF is now available, particularly in the presence of anatomic variations[156]. This technology provides precise anatomical structure customize to each patient's specific anatomy and ablation point delivery to improve success and patient safety in AF ablation. In Bordeaux, CT segmentation using CartoMerge module is used to create the anatomy to guide AF ablation in challenging cases.

Therefore, mapping and navigation system is useful for AF ablation to construct the LA/PV geometry and visualize catheter movement in real time for pulmonary veins isolation or substrate modification (linear ablations). In addition, the mapping and navigation system allow documentation of the electrical ablation end point and diagnosis, and ablation of non-venous atrial triggers initiating AF, enhancing safety, efficacy and improving outcome of the procedure.



Figure 12: Three-dimensional maps generated by the Carto 3 system show the location and orientation of catheters in the heart[157].

Non-invasive body surface electrocardiographic mapping

A 3-D, body surface imaging and mapping modality (ECVUETM, Cardioinsight Technologies) are now available[158]. Non-invasive mapping for persistent AF (PsAF) guides catheter ablation[159] by visualizing AF drivers in panoramic beat-to-beat mapping and enables understanding of dynamic AF mechanisms. A 252-electrode vest is applied to the patient's torso and connected to the non-invasive imaging system, and surface potentials are recorded followed by a non-contrast thoracic CT scan to obtain high-resolution images (64 sections) of the heart and the vest electrodes. The 3-D epicardial bicameral atrial geometries are reconstructed from segmental CT images. The system reconstructs

epicardial potentials, unipolar electrograms and activation maps from torso potentials during each beat/cycle using mathematical reconstruction algorithms[160-163]. AF electrograms are acquired during a long ventricular pause (spontaneous or diltiazem-provoked). QRS is subtracted and AF maps are created using specific algorithms combining wavelet transform and phase mapping applied to the reconstructed epicardial potentials. Activation maps are computed using traditional unipolar electrogram intrinsic deflection-based (dV/dT) max method. AF analyses identified localized re-entrant (rotor) and focal sources driving and maintain AF[164, 165]. The number of foci and re-entry through the total duration of all windows are displayed and cumulative driver-density maps[159] (figure 13). AF termination after driver-guided ablation was 63% [159].



Figure 13: (A) After acquiring CT scan with the 252-electrode vest; (B) multiple atrial fibrillation (AF) windows with subtraction of QRST are analyzed to identify consistent drivers by using phase map analysis. (C) The cumulative epicardial driver map is composed on the reconstructed biatrial shell from CT. Density of the driver map is based on the prevalence and trajectory of the reentrant driver core. AP = anterior–posterior; PA = posterior–anterior[159].

Cardiac Imaging (CT/MRI)

Three-dimensional (3D) computed tomography (CT) and magnetic resonance imaging (MRI) angiography are now commonly used to plan and guide AF ablation. CT and MRI imaging help understand the variable nature of PV anatomy in relation to surrounding structures to identify any technical difficulties (in particular common ostium and atypical position of the oesophagus, respectively); exclude LA or LAA thrombus; provide detailed atrial tissue characteristics such as fibrosis (substrate), pericardial fat, and local wall thickness providing additional information for patient selection and ablation strategies; evaluate post-procedure complication such as PV stenosis and esophageal injury and guide additional ablation to fill in 'gaps' in recovered PV conduction[166, 167]. These modalities are commonly incorporated into electroanatomic mapping systems to guide ablation lesions placement and reduce fluoroscopic radiation exposure[166].

CT and MRI appear to characterize complex LA anatomy better than 2D imaging modalities such as fluoroscopy and echocardiography[168, 169]. Both modalities provide similar information before catheter ablation to characterize LA anatomy; however, MR is associated with lower overall cumulative radiation despite similar outcome in comparison with CT[170], although MR has the advantage of not exposing patients to high doses of per-procedural radiation, does not require iodinated contrast media and provides better contrast, the spatial resolution and the quality of the 3D reconstructions is slightly poorer with MR than with CT [167]. In many centers, CT of the PV is the gold standard and

MR is an alternative as a second line pre-procedural technique[167]. However, some centers use MR as the first line technique with 99% of diagnostic scans and 90% of very good quality scans[171].

Delayed gadolinium enhancement MRI (DEMRI) shows promise as a more direct method of assessing pre-procedure atrial fibrotic changes for evaluating arrhythmogenic atrial substrate and ablation patient selection[172, 173]. DEMRI is based on the preferential retention of intravenous gadolinium contrast within myocardium that has disrupted vasculature[172]. MR has the most established history for assessing lesion characteristics following cardiac ablation because of the high-resolution atrial ablation lesion imaging following PVI using DEMRI [174-177]. The difficulty of transporting patients between the electrophysiology (EP) lab and MR scanner limits the practicality of using DEMRI lesion imaging for guiding ablation. This limitation is one motivation for research into performing ablation procedures within the MR scanner using real-time MR guidance[174, 178-180]. Lesion visualization using other modalities that are more amenable to intra-procedure integration is also under investigation such as C-arm[181] CT and intracardiac echocardiography (ICE)[182, 183].

CT and MR have relative advantages and disadvantages. CT has the advantage of short imaging times and high spatial resolution[166]. Current CT systems are capable of generating 3D angiograms with $0.5 \times 0.5 \times 0.5 \times 0.5$ mm resolution within around 10 heart beats for 64 detector systems and within one heart beat for 320 detector systems[184]. In contrast, 20 to 30 seconds breath hold is typically required for 3D MR with a voxel resolution around 1.5 x 1.5 x 1.5mm[166]. More significantly, much longer imaging times of several minutes are currently required for 'fibrosis' and ablation lesions DEMRI studies. Other advantages of MRI over CT is that it does not require ionizing radiation and it has more flexible soft tissue contrast to evaluate atrial substrate and ablation lesions[166].

Cardiac magnetic resonance imaging (CMR)

Cardiovascular magnetic resonance (CMR) provides non-invasive imaging modality that allows identification of myocardial scar [185-187] and edema[187] using late gadolinium enhancement (LGE) and T2-weighted (T2w) imaging, respectively. The role of MRI in AF ablation is variable. In pre-ablation, MRI is a non-invasive and accurate modality to assess LA and PV anatomy, measure LA volume [188, 189] and detect atrial fibrosis[173]. DEMRI resonance imaging can identify LA wall structural remodeling (SRM) by stage (I-IV) based on the percentage of LA wall enhancement for AF patients stratification and ablation outcome prediction, in addition to displaying extensive LGE (\geq 30% LA wall enhancement, stage IV patients) predicts > 70% poor response to AF catheter ablation and therefore AF recurrence [190]. Atrial fibrosis in PsAF detected by DEMRI and high-density mapping is associated with slower and more organized electrical activity (ablation non-target sites) whereas continuous complex fractionated atrial electrogram CFAE sites (ablation target-sites) occurred at non DEMRI and patchy DEMRI sites[191]. In fact, DEMRI is designed to evaluate focal scar after myocardial infarction, pending issues of atrial fibrosis on MRI reproducibility of acquisition and quantification bring up some concerns. In post-ablation, MRI provides assessment of early (24-hour) ablation induced edema and injury/necrosis (increased LA wall thickening) following pulmonary vein isolation (PVI) to predict LGE later scarring (30-days), with high sensitivity (91% and 82%) but lower specificity (47% and 63%) for both 24-hour LGE and T2w imaging, respectively, where the low specificity suggests that some acute injury resolves [192] (figure 14). In addition, MRI assesses the effect of atrial fibrosis (at baseline and residual fibrosis (pre-ablation atrial fibrosis not covered by ablation scar) and ablation-induced scars on catheter ablation outcomes predicting 35% of AF recurrences because of fibrosis uncovered by ablation scar[192, 193].



Figure 14: DEMRI showing LGE related to scar after PVI in LA (yellow arrows).

Ablation procedure

Ablation approaches for AF can be divided into two major strategies: electrically guided ablation (segmental or ostial)[194-203] and anatomic ablation [204-212]. Electrically guided ablation either by single tip point-by-point or circular catheter ablations for achieving either ostial (segmental) PVI (triggers elimination) in PAF patients or circumferential PVI (triggers and substrate elimination) in PsAF patients[204-212] (figure 15). Ostial isolation, in which a selective ablation of PV potentials at the PV ostium providing PV disconnection with minimal ablation[75, 194][75, 194], and wide antral PVI, which involves ablation of wider area of PV-LA junction encompasses part of the LA posterior wall. [202]. PVI performed with a wide antral approach (more extensive ablation) is more effective than ostial PVI in achieving freedom from total atrial tachyarrhythmia recurrences at long term follow-up due to the elimination of triggered activity, mother waves near the PV ostium that drive AF and vagal denervation [84, 206, 210, 212-214]. With regards to the incidence of major complications, a systematic analysis shows no difference was detected between the 2-ablation strategies [213]. The relative merits and potential limitations of each approach are debatable and structural anatomic variability may have potential implications regarding the choice of an ablation approach[215, 216]. The mechanisms of AF are complex and not yet well defined. Based on multiple AF mechanisms ablation strategies target either the driverswhether they originated within the PV[86, 217, 218], LA[219-222], or elsewhere[223]- or the LA substrate modification including rotors, autonomic tone, and mother wavelets [164, 210, 224].



Figure 15: Antral (anatomical) versus ostial PVI ablation and AF pathophysiology[225]. PV = pulmonary vein, LA = left atrium, WACA = wide antral circumferential ablation, LOM = ligament of Marshall, AG = autonomic ganglia.
Pulmonary vein isolation

Curative ablation of AF is limited to patients who remain symptomatic despite the use of antiarrhythmic drugs (AADs). PVI alone achieves the best benefit in patients with short episodes (< 24 hours) of PAF with no structural heart disease and normal LA size[85]. Single-procedure efficacy ranging between 50% and 75% [226]. However, patients with structural heart disease establish more persistent or permanent AF where PVI has limited role to clinically suppress the arrhythmia and therefore additional non-PV ablations are sometimes required [196, 227-229].



Figure 16: Lasso catheter: positioned within the pulmonary vein (PV) to identify PV signals. Ablation catheter positioned to ablate within the left atrium.

Ablation is performed by chasing PV potentials that signify the location and extent of the local striated muscle and electrically connects the PV to the LA[194] (figure 17). PV potentials targets are sharp, of high frequency, and of short duration (< 50 msec) and differentiated from far-fields atrial potentials by comparing the activation timing relative to adjacent structures and by pacing from these structures [219, 230]. Atriovenous electrical disconnection is demonstrated by elimination of PV ostial potentials by mapping and the absence of discrete electrical activity inside the lesion during pacing outside the ablation line [205].

Sequential and circumferential mapping and ablation at the PV-LA connection sites of the earliest PV activity, can be electrically isolated from the LA especially and the site of change in PV activation (sites represent critical connections between PV and LA) by applying longer radiofrequency (RF) energy. When ablation, infringement of the PV is frequently required to achieve catheter stability in challenging areas such as the anterior and the inferior aspects (ridge, separating the left PV from the appendage, is relatively narrow) of the left PVs. Other target sites for ablation include: atrial ectopy triggering AF, very-high frequency atrial activation driving to maintain AF).



Figure 17: Disappearance of pulmonary vein potentials during segmental pulmonary vein ablation. Filled arrows indicate sharp potentials recorded at ostium of left superior pulmonary vein by a decapolar Lasso catheter. Pulmonary vein angiography via a multipurpose catheter placed within the vein demonstrates correct placement of Lasso catheter ostium. During radiofrequency ablation delivery at the ostium (catheter not shown), pulmonary vein potentials disappeared (empty arrow). CS indicates coronary sinus; MAP, bipolar signals from quadripolar mapping and ablation catheter; and PV, bipolar signals from Lasso catheter[231].

At our institution, circumferential mapping is performed with the Lasso catheter (Biosense Webster, Diamond Nar, Calif.) under fluoroscopic and Carto system guidance. Ablation is performed exclusively with an externally irrigated ablation catheter to ensure delivery of the desired power with lower risk of char or coagulum and consequently reducing the risk of embolic events during ablation. Circumferential ablation is performed with longer application at critical sites of the PV-LA connections. These sites are identified by the earliest PV activity during antegrade conduction into the vein, or as sites at which a change in PV activation occurs during ablation. Targeting these sites with longer RF duration reduces the recurrence of PV. Fluoroscopic landmarks are helpful during ablation to localize PV-LA junction, to the right and left border of the spine (in the antero-posterior (AP) projection), staying along this border in general ensures that ablation is atrial (1 cm away from both right and left PVs) and thereby, minimizes the risk of PV stenosis. Ablation parameters are: power delivery of 30-35 W (reduced to 25-30 W during ablation within the PV or posterior wall), RF duration at each point is 30-60 seconds and up to 1-2 minutes if PV activation changes, target temperature of 50 °C and irrigation rate is adjusted between 5 and 20 mL/minute. Additional ostial applications targeting fragmented electrograms (more than two deflections) are performed after PVI to eliminate ostial PV potentials and therapy reduce the risk of recurrence.

PV electrical isolation (elimination or dissociation of PV potentials) provides a defined procedural end point (achieved in 100% of patients). End points for ablation of AF are assessed by entrance and exit block electrical isolation of all PVs by pacing with the use of adenosine injection 30 minutes of PVI. Data from our institution demonstrate the PVI is achieved within 35 minutes of RF application with 44 minutes fluoroscopy and 70 procedural duration times[232]. Immediate procedural success range from 82% to 100%[85, 203, 233, 234]; however, 27% to 48% of patients develop early recurrence (within days) of AF and, therefore, have a significantly lower long-term success rate, caused by PV-LA recovery conduction of the previously isolated PV and by non-PV foci [85, 87, 234]. Additional ablation using lines during a second procedure if PVI is still complete is performed in up to 30% of AF recurrence[210, 228, 229, 235]. In addition, in a select subset of patients with persistent or permanent AF, ablation of the PVs has limited effect and, therefore, additional substrate modification ablation is required[196, 227-229].

Non-pulmonary vein ablation

Ectopies originating from non-PV areas can result in AF in 14% to 28% of patients, and in addition lead to the recurrence of AF in more than 24% of patients after PVI [75, 196, 217, 236-249]. Highlighting the importance of utilizing non-PV ablation after multiple procedures to significantly lower the recurrence rate and achieve an overall higher success rate.[234, 250]. The characteristic anatomic distribution of non-PV ectopies are: superior vena cava (SVC), left posterior free wall, crista terminalis (CT), coronary sinus ostium (CS), ligament of Marshall, and interatrial septum respectively [246, 248, 249](figure 18).



Figure 18: The distribution of non-pulmonary vein foci (NPVF) in primary (PVI) (A) and repeated procedure (AF recurrence, reconnected PV and NPVF) (B) in right and left atria, showing the development of NPVF in AF recurrence after PVI [251]. AP = antero-posterior view, PA = postero-anterior view, TA = tricuspid annulus, MA = mitral annulus.

Ectopic focus is analyzed and mapped by 3-D guided Carto mapping of the P-wave polarity at the earliest activation sites and endocardial activation sequence [252]. Mapping-guided ablation technique for the elimination and electrical isolation of non-PV AF initiators is the site that shows earliest bipolar deflection or unipolar QS pattern recorded from the ectopic foci preceding AF[217, 236, 237, 239, 246].

Radiofrequency energy with temperature control (50 °C to 55 °C) is delivered for 20-40 seconds and required to produce irreversible thermal injury[253-256].

Non-isthmus-dependant atrial flutters and atrial macroreentry ablation

Atypical atrial flutter (AFL) coexist with AF and may play transitional roles in the initiation or termination of AF in the transformation to atypical AFL. Proof of a macroreentrant mechanisms can be obtained through manifest entrainement[257] (figure 19), concealed entrainment or electroanatomic mapping. Activation mapping is performed to demonstrate early or mid-diastolic potentials, fractionated potentials, and double potentials. Concealed entarinment demonstarte participation in the tachycardia circuit[258]. Electroanatomic mapping (Carto) is used to visulaize the reentrant circuit. Double-loop reentry (or multiple-loop reentry) should be recognized as a common variant of left atrial tachycardias, and a common segment should be identified. Typical sites of ablation include the following: (1) from the left pulmonary veins to the mitral isthmus (the mitral isthmus), (2) from the right pumonary veins to the mitral anulus, (3) from the pulmonary vein to an electrically silent area in the posterior wall, and (4) between two electrically silent areas in the posterior wall or roof of the LA. The guiding principle in ablating macroreentrant atrial tachycardia is to target a critical isthmus that participate in the tachcardia circuite. The technique of ablation involves the creation of a linear lesion between two bounderies to transect the isthmus[259]. Electrogram reduction at sites of effective ablation, and ideally, conduction block should be verified after ablation by pacing on one side of the ablation line and recording from the other side (bidirectional block[260-262]. Double potentials, as well as the absence of atrial elctrograms, along the ablation line prvide supporting evidence for conduction block after ablation. For instance, verification of a line block along the mitral isthmus can be demonstrated by pacing distal and proximal the the ablation line, using one catheter in the CS and one in the LA. Bidirectional block for rooF line is confirmed by differential pacing from LA appendage cersus LA posterior wall (LAPW)[263]. To distinguish slow conduction from complete block, the technique of differential pacing may be used. This involves compating times during pacing from distal and proximal poles of a CS catheter. If complete conduction block is present, clockwise conduction time around the mitral annulus is longer with distal pacing than with proximal pacing (figure 20). Completion of the ablation line in the mitral isthmus may be difficult to achieve and may require ablation within the CS with an irrigated-tip catheter.[229] The long-term recurrenc rates of atrial arrhythmias after ablation are unknown, because atypical AFLs are associated with other atrial arrhythmias and AF.



Figure 19: Electroanatomic map of the left atrium during flutter. A large area of scar is noted along the posterior left atrium (right map). Activation mapping demonstrates a counter-clockwise peri-mitral macro-reentry. Entrainment demonstrates the best post pacing interval (PPI) at the lateral mitral isthmus[264].



Figure 20: Anteroposterior view with a schematic representation of the mitral annulus (MA), right and left pulmonary vein (PV), left atrial appendage (LAA), and mitral isthmus (MI) line (pair of broken white lines). Decapolar catheter is inserted into the coronary sinus (CS), and ablation catheter is placed on the MI line. The perimitral conduction time (PMCT, circular arrow) was evaluated by pacing septal to the line of block (pacing sign) and recording the second late potential (red arrow) on the line of block. RF indicates radiofrequency[265].

Complex fractionated atrial electrogram (CFAE) ablation

Additional ablation to PVI targeting is that of complex fractionated atrial electrograms (CFAE) by performing high density mapping of LA using Carto system (CFE mean used to <80 msec, measuring more continuously fractionated signals compared to CFE mean <120 msec including intermittent electrogram fractionation (EGM) during AF) which is associated with higher acute and long-term success rates in patients with PsAF[266-268] (figure 21). Different electrophysiological mechanisms including focal discharge, wave break and fusion associated with slow conduction and pivoting activation in the CFAE region sustain wave propagation and resulting in AF maintenance [269]; result in CFAE[270]; and complex EGMs can either actively contribute to AF perpetuation or passively as bystanders as a result of 'wavelet collisions', suggesting absence of myocardial fibrosis or scar and therefore unlikely to represent effective targets for ablation [268, 271, 272]. In our institution, we use an algorithm with criteria estimating the degree of fragmentation based on taking a sample of interested signals for 2.5 seconds targeting and mapping CFAE signals that have amplitude between 30 ms and 120 ms, a rapid cycle with fragmented signal (CL < 120ms) with at least two deflections crossing the base line. The ablation of continuous CFAE sites is associated with prolongation of AF cycle length and termination of AF comparing to intermittent CFAE sites [273] however, some CFAE sites do not have impact on AF cycle length demonstrating that not all CFAE play a role in AF perpetuation or are appropriate targets for ablation.[274]. The extent of CFAE on PsAF versus PAF was 28 ± 4% and 16 ± 4%, respectively [268]. Continuous CFAE sites at LA regions were associated with non-DEMRI regions and most of dense DE sites did not display CFAE but slower, low-voltage electrical activity [191] (figure 22). The region of slow conduction (with fractionated or rapid activity) within or around the areas of atrial fibrosis are promising ablation target in patients with persistent

AF[191].



Figure 21: continuously fractionated signals.



Figure 22: Relationship of atrial DE to continuous CFAE sites. Examples showing relationship between dense DE, patchy DE and continuous CFAE sites (CFEmean <80ms) from 2 patients with long-persistent[191].

Driver based-ablation[159]

In non-invasive mapping-guided ablation, the cumulative driver map determines the order of ablation sites. After acquiring atrial geometry on 3D-electroanatomical mapping system (Carto 3, Biosense Webster Inc.), the region having the highest density of re-entrant drivers is targeted first followed by the region with the second-highest driver density and so on (figure 23). Within the driver area, rapid and continuous fragmented signals and activation gradient between proximal and distal electrodes are locally mapped and targeted for ablation[275]. The endpoint of RF application is elimination of fragmented potential and slowing of the AF cycle length at the local site. Each RF application targets dominant clusters of AF driver at 30-40 W (25 W in posterior wall) using an ablation catheter with a temperature cutoff at 45 °C. If AF persists after ablation of the first targeted region, the second-highest area of driver is subsequently ablated in the same way. The end point of the procedure is AF termination (sinus rhythm SR or AT), or completion of RF applications targeting all driver areas. If the drivers are present around PVs, PVI is routinely performed. If AF sustained after driver-based ablation, electrocardioversion is performed.



Figure 23: (A) Targeted signal and endpoint of local radiofrequency (RF) application. The rapid and fragmented potentials in the driver area are targeted. The endpoint of RF application is organization of the local fragmented signals and slowing of the local AF cycle length at the RF site. (B) A typical example of driver-based ablation. In this case, based on the body surface mapping result, left atrial inferior was targeted at first because of high density of reentrant drivers and the fact that fragmented activities were observed in the coronary sinus, left atrial septum; ridge and anterior were then followed. Finally, atrial fibrillation terminated at left atrial anterior (blue spot).

Complications

While having relative success in clinic and being a minimally invasive procedure, there are a number of complications that can arise as a result of ablation therapy. Five to seven per cent of patients will suffer severe complications after catheter ablation of AF, and 2-3% will experience life-threatening but usually manageable complications[276-279]. Intraprocedural death is (< 0.2%)[280]. The most important severe complications are stroke/TIA (< 1%), cardiac tamponade (1-2%), pulmonary vein stenosis, and atrio-oesophageal fistula[1]. One of the most concerning complications of these procedures is PV stenosis[281] (figure 24). The current incidence of angiographic PV stenosis (> 50% reduction in PV diameter) is less than 2%, with most patients being asymptomatic.



Figure 24: The 3-D images of the left atrium (posteroanterior and top view) constructed by multidetector computed tomography after the procedure demonstrated severe left superior pulmonary vein (LSPV) stenosis immediately posterior to the persistent left superior vena cava (PLSVC)[282].

Ablation anywhere within the atria can result in the creation of conduction abnormalities that then able to anchor re-entry. After PVI alone, 12% of patients have inducible macroreentry, and 5% present with spontaneous macroreentry[283]. Mapping and ablation demonstrated that these arrhythmias use the ablated zone as a central obstacle, resulting in either perimitral or peri-PV re-entry, the later being more prevalent in patients with larger atrial[283, 284]. More recently, atrial-oesophageal fistula (AEF) often associated with a fatal outcome is reposted[211, 285-287]. This complication was observed in patients undergoing anatomic ablation strategy or nMARQ circular ablation catheter, with high power delivered along the posterior wall. Anatomical and procedural contributing factors play a role in the pathogenesis of AEF, such as small LA (because the oesophagus occupy a larger relative area of the posterior LA, where part of ablation is performed)[288] and direct thermal injury during ablation (related to catheter tip size and or orientation, contact pressure, posterior wall lesions, and power output and duration[289-291], respectively. AEF could be avoided by using bipolar RF mode that is safer than unipolar mode, hypothetically- prevents energy dispersion and thus the formation of AEF[292], lower power setting and shorter lesion durations in the posterior LA using an open-irrigated catheters[293]. The integration of CT scan or MRI and Carto 3 provides an accurate visualization tool to understand the anatomy before ablation[294].

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ABLATION CATHTER TECHNOLOGIES AND CHALLENGES OF ATRIAL FIBRIILATION

Due to inadequate efficacy of pharmacological therapy and a plethora of side effects, catheter ablation of atrial fibrillation (AF) has evolved dramatically over the last decade, electrophysiologists were eager to obtain high success rates with extensive ablation[295]. Today research has focused on gaining further clarification of the complex mechanisms of AF to make AF ablation safer and more efficient[295]. With better understanding of AF pathogenesis, new technologies, experience and research, limitations and challenges are being overcome.

Catheter ablation history

The first intentional catheter ablation in humans was performed by Dr Melvin Scheinman (cardiac electrophysiologist in San Francisco, California) in 1981, using high-energy direct current shocks[296]. Dr Scheinman's work led directly to the development of radiofrequency energy (RF) catheters to perform more precise ablation. At the beginning, catheter ablation was used for focal arrhythmia sources or pathways, such atrio-ventricular nodal re-entrant tachycardia (AVNRT) or Wolff-Parkinson White syndrome (WPW). However, only over the past decade, catheter ablation was used to treat more complex rhythms like AF.

In 1998, Prof Michel Haissaguerre (cardiac electrophysiologist in Bordeaux, France), first described the use of catheter ablation for patients with AF, ablation catheters were inserted in human hearts for pulmonary vein isolation (PVI) mapping and ablation[75] and lead to the

development of catheter ablation as a routine management strategy for AF. The initial ablation strategy was to map and ablate the individual triggers inside the pulmonary vein (PV) ectopies but this strategy was associated with high recurrence rate and risk of PV stenosis[75] (figure 1). In 2000, Prof Haissaguerre described a new approach for PVI by using a circular mapping catheter with multiple electrodes that allows sequential assessment of PV potentials to guide PVI[297] (figure 2).



Figure 1: Diagram of the sites of 69 foci triggering atrial fibrillation in 45 Patients[75].



Figure 2: Circular mapping catheters used for electrical PVI[296].

Since 2001, several incremental improvements in the PVI approach were developed from (1) segmental (ostial): first catheter-based technique to electrically isolate the PVs[201, 205], - to (11) circumferential (antral) PVI, so called wide area circumferential ablation (WACA defined as circumferential isolation performed at least 1.5 cm away from the PV ostium as defined by angiography or 3-dimentional (3D) electoanatominal reconstruction[213]) involving more triggers and drivers (structures and substrates) other than PV such as, antral region of the PVs, the vein and ligament of Marshall, and the posterior LA wall, in addition to denervation ablation [298, 299] (figure 3), the Longterm success rates for segmental approach are relatively modest (60-70%). Initial evaluation showing comparable success rates (75%) was found using circumferential approach compared to ostial approach[300]. However, a systematic review comparing the effectiveness of WACA versus ostial PVI showing that WACA is more effective than ostial PVI with reduction in fluoroscopy time but with longer total procedural time[213]. With regards to the incidence of major complications, no difference was detected between the 2 ablations strategies[213]. Several factors explain the potential advantage of wide antral PV: (1) elimination of reentry wavelets localized around the PV antrum, (2) autonomic denervation, (3) PVI, (4) extensive LA debulking, and (5) non-PV foci ablation localized in the posterior LA wall [213].



Figure 3: Ostial versus wide antral PVI anatomical landmark[225].

Because of complex and unclear persistent atrial fibrillation (PsAF) mechanisms and low ablation efficiency, other mapping and ablation strategies were developed to modify left atrium (LA) substrates that stabilize the maintenance of AF. Two other techniques additional to

PVI[196, 227] were described for PsAF ablation: (1) ablation based on electrogram analysis (figure 4) [266, 301-303] and (11) LA linear lesions (figure 5) [214, 229, 304-308]. The combination of PVI and either electrogram-based ablation or LA lines showed to increase the efficacy of catheter ablation for PAF and PsAF[214, 229, 304-310]. AF Substrate mapping and ablation, so called complex fractionated atrial electrograms 'CFAEs' ablations (targeting electrograms with a cycle length (CL) of more than 120ms, or shorter) was developed in 2004 and resulted in AF termination in \approx 95% of patients with an improved clinical outcome, in which 90% of patients were reported to be free from recurrent arrhythmias [266]. CFAE ablation in conjunction with PV antral isolation has a higher likelihood of maintaining sinus rhythm compared with PV antral isolation alone in patients with PsAF[311]. The major problem concerning CFAE ablation is that the definition of CAFEs is arbitrary and subjective[295]. Although some studies attempted to objectively detect CFAEs with custom software and demonstrate differences in the distribution of CFAEs in the LA between PAF and PsAF[312, 313], the impact of the objective definition on clinical outcomes is unclear[295]. The very high prevalence of CFAEs in the LA suggests that CFAEs alone are a nonspecific marker of appropriate target sites for ablation[314]. Therefore, the value of CFAEs ablation remains controversial. PsAF is much more likely to convert to atrial tachycardia (AT) rather than to sinus rhythm (SR) during ablation and AT is common after catheter ablation. The prevalence of AT in patients undergoing circumferential PVI at follow up was reported to be 24%, caused by a re-entrant mechanism (mitral isthmus, roof and septum accounted for 75% of the ablation target sites), mainly mitral isthmus-dependent flutter as primary arrhythmia[315, 316]. However, it is suggested that the AT occurs during catheter ablation of AF is a driver of AF that manifests after elimination of fibrillatory conduction[317]. The ideal endpoint of linear ablation is complete electrical block[214, 229, 318-320], however, this is technically challenging to achieve bidirectional block (BDB), time consuming, potentially hazardous and proarrhythmic if it is incomplete[214, 229, 263, 321-323]. By 2013, non-invasive mapping was developed to identify AF drivers to guide catheter ablation and promises equivalent clinical results with less RF time used to achieve AF termination with lesser tissue damage compared to stepwise ablation[159] (Stepwise ablation approach described in 2006[324], broadly divided into: PVI, roof, LA (incorporating all anatomic regions of the chamber), mitral isthmus and non-LA structures, each region is targeted in sequence and the impact of ablation upon the global fibrillatory process assessed by measurement of AF cycle length (AFCL) at a site remote from the ablation target). After PVI and demonstrable complete conduction block across the roof and mitral isthmus lines (when performed), ablation is performed at those sites displaying continuous electrical and complex fractionated activity, with the endpoint of local organization, as well as at sites displaying electrograms consistent with focal sources driving AF [78, 158, 159, 324].



Figure 4: Complex fractionated atrial electrograms (CFAE) using Ensite NavX automated software displays activation timing and voltage data (St. Jude Medical). Left: Anterior view of the left atrium showing predominant location of CFAEs over anterior wall and the roof. Right: Posterior view of the left atrium showing the ablation lesion sets (red dots) for pulmonary vein isolation and the left atrial posterior wall[325].



Figure 5: Electroanatomic maps of the left atrium after AF (left lateral view (left) and postero-anterior view (right). The left superior (LSPV), left inferior (LIPV), right superior (RSPV), and right inferior (RIPV) pulmonary veins are labeled. The continuous series of solid red circles encircling the pulmonary veins represent radiofrequency ablation sites. Two additional linear lesion sets are shown: one connecting the two circular lesions that surround the pulmonary veins (posterior line), and one connecting the mitral valve annulus to the circular lesion that surrounds the left pulmonary veins (mitral isthmus line)[326].

Catheter ablation energy sources

The goal of any catheter ablation is to accurately identify targeted signal for ablation and to create a transmural lesion effectively and safely.

Catheter ablation is aimed to create permanent irreversible destruction of abnormal cardiac tissue that causes cardiac arrhythmogenesis

while preserving collateral tissue injury. Transmural lesions depend on the temperature generated by the energy source, the catheter-tissue

contact, and catheter stability on target tissue. There exist different energy sources used in ablation, and each has advantages and limitations. Energy sources could be divided into two major categories: heat based such as radiofrequency and laser, and cold/freezing based such as cryo.

Heat based ablation by radiofrequency (RF) energy is radio wave (similar to microwave heat) that are converted to heat to ablate and create lesions that transform into scars. Radiofrequency current for catheter ablation is an alternating current using resistive heating that is delivered at cycle lengths of 300 to 750 kHz[327] [328]. It reliably achieves transmurality and is the most widely used energy source in catheter ablations. The degree of tissue heating is inversely proportional to the radius to the fourth power[329], the lesions created by RF energy are small. Typical ablation catheters, which are 2.2 mm in diameter (7 French (F) = 0,23 cm) and have a distal electrode of 4 mm long, create lesions approximately 5 to 6 mm in diameter and 2 to 3 mm deep[330, 331]. Larger lesions are possible with larger electrodes or irrigated ablation catheters[332]. Irreversible tissue destructions requires a tissue temperature of approximately 50 °C[255], adjusted manually or automatically by the RF generator to achieve a temperature of 60 to 75 °C at electrode-tissue interface[333]. High temperature at 100 °C form coagulum, prevent effective current delivery and therefore predispose the patients to thromboembolic complications[334].

The acute lesion created by RF current consists of a central zone of coagulation necrosis surrounded by a zone of hemorrhage and inflammation. Chronic lesions are characterized by coagulation necrosis and have a discrete border[335]. Resolving inflammation in the border zone of the lesion without residual necrosis explains arrhythmia recurrence several days to several weeks after apparently successful ablation[327, 336].

Cryoablation, or cryo energy results in tissue injury though the generation of extremely low temperature (between -30 to -90 °C)[337]. At temperatures reaching -20 °C, extracellular ice formation occurs resulting in an osmotic shift of water from inside the cell to out[337]. At lower temperatures still, intracellular organelle and vascular structures damage occur as well as hyperthermia from rewarming contribute to tissue[337]. The net result is tissue destruction with sharply delineated lesions that preserve underlying tissue and extracellular matrix architecture[338]. The hypothermic tissue injury induced by cryoablation is nonthrombogenic [339, 340]. Historically, at the beginning of using this alternative source of ablation, cryoenergy was used successfully in ablating atrioventricular nodes[341] and supraventricular tachycardias[342]. In the early 2000's, several investigators examined the feasibility of using focal cryoablation catheters for PVI and showed that cryoablation for PVI was effective and safe but associated with a frequent need for a repeated procedure[343]. In 2005, cryoballoon technology using a 23 mm balloon was successful in isolating 83% of PV[344]. Briefly, this technology utilizes a cryoballoon catheter placed in the LA following a transeptal access via a 12 French inner/15 French outer deflectable catheter over a 0.035 inch guide wire via a femoral

access[337]. The Arctic FrontTM balloon is available in two diameters (23 mm and 28 mm). The guide wire is placed in branches of the target PV and the inflated balloon is advanced over the wire to the ostium of the vein. Contrast can be injected through the catheter to assess for complete venous occlusion. Nitrous oxide (N2O) is delivered into the balloon and freezing times range from 240-300 seconds per freeze. To assess for PVI without the need of a second transeptal access, the AchieveTM catheter was developed. This catheter is an 8-pole lasso that can be deployed through the guide wire lumen and hence advanced into the vein with the Arctic FrontTM catheter in place. The freezing procedure is repeated sub-selecting different PV branches for all four veins until complete isolation of all veins is achieved. Recently, a second generation cryoballoon was introduced with the goal of isolating each PV with fewer number of freeze applications. The first generation ArcticeFrontTM balloon catheter utilized four injection ports through which N2O refrigerant was sprayed in a region of the balloon just distal to the equator and this resulted in a gradient of cooling such a higher temperature were seen at the distal poles of the balloon compared to the equator[345, 346]. In the second-generation cryoballoon, the coolant was directed homogeneously in the distal half of the balloon in the hopes of remedying this problem. When compared with the first-generation balloon, the second-generation design showed improved first freeze isolation and shorter procedural times [347, 348]. While an improved procedural and mid-term efficacy has been welcomed the safety profile of the new cryoballoon needs further investigation. Several studies on procedure outcome were studies and showed successful PVI that was ranging from 84% to 98% [344, 349-352]. At 12 months, the freedom from detectable AF was achieved in 97% of patients randomized to the cryoballoon group and 7.3% in patients randomized to anti-arrhythmic drugs group [352]. Concerning the

complications of cryoablation, previous literatures identifies phrenic nerve injury during right pulmonary vein (RPVs) ablation as the most frequent complication[353-358]. Careful monitoring of the phrenic nerve during freezes of the RPVs by pacing from superior vena cava (SVC) to stimulate phrenic nerve (hence assess functionality in real-time) [359-363] and immediate balloon deflation[364] were described to help detect phrenic nerve paralysis or injury (PNI). Oesophageal probe to monitor oesophageal temperature during the freezes is recommended as well as in RF ablation procedures to monitor the oesophagus and prevent atrio-oesophageal (AE) fistula [365-369].

RF ablation versus cryoablation (figure 6), there are several differences between both technologies in lesion formations and thromboembolic risk concern. Histologically, on qualitative analysis in mongrel dogs[338], cryolesions were well-circumscribed discrete lesions with sharp borders, dense areas of fibrotic tissue, and contraction band necrosis (figure 7). In contrast, RF lesions were characterized by intralesional hemorrhage and ragged edges less clearly demarcated from the underlying normal myocardium[338]. Moreover, replacement fibrosis confined to the outer margin of RF lesions but not cryolesions suggests a slower post-ablation healing response to RF energy[338]. In addition, RF ablation resulted in lesions of greater area (p = 0.0018) and nearly significantly larger volume (p = 0.0585) but not in depth compared with cryoablation that was associated with deeper lesions by colder temperature[338]. Technically, compared with traditional RF energy, cryoablation for PVI has several potential advantages[337]. First, cryoablation is associated with less patient discomfort than RF, a characteristic that is particularly advantageous in centers where PVI is performed under conscious sedation rather

than general anesthesia. Second, the use of cryo-ablative catheters results in freeze-mediated catheter adhesion, a trait that can enhance catheter stability particularly in traditionally challenging areas to ablate such as the ridge between the left atrial appendage and left sided PV. Lastly, cryoablation has been shown to be associated with less platelet and coagulation cascade activation leading to a lower risk of thrombus formation [370, 371]. It had been postulated that one of the benefits of cryoablation PVI compared with RF is associated with lower risk of atrio-oesophageal (AE) fistula formation, a severe but rare complications seen in RF PVI procedures [337], though esophageal ulcers and AE fistulas with cryoablation was reported [372-374]. Currently, in real world practice, at least in the hand of experienced operators the overall complication rates seem to be comparable between RF and cryoballoon ablation, however type of complications varies significantly[375, 376]. Other potential advantages of cryoablation compared with RF PVI, including shorter procedure time[350, 377, 378], decreased hospitalization duration[377] and decreased fluoroscopy time[350]. Despite the cryoablation advantages, RF was the first technology approved for AF ablation and has the longest track records. The availability of other advancing technologies in RF catheter ablation such as contact force sensing and circular catheters is allowing more consistent and durable lesion formation. Although PVI is the cornerstone for treating AF, cryoablation is designed only for PV ablation and therefore has no therapeutic benefits in patients with non-PV triggers and/ or atrial flutters.



Figure 6: Two main techniques are currently used to perform PVI: traditional radiofrequency catheter ablation (left) and cryoablation (right)[379].



Figure 7: Histology of cryoenergy and RF lesions. Typical histological characteristics 1 week after cryoenergy (A) and RF (B) ablation when stained with Masson's trichrome and magnified 16-fold. Note more homogeneous nature of cryolesion, with a smoother, sharper demarcation from intact myocardium (A). In contrast, RF lesion is less well circumscribed, with serrated edges (B). Arrow indicates endocardial thrombus formation at ablation site[338].

Laser balloon catheter, recently, the CardiofocusTM endoscopic ablation system was introduced in Europe as an alternative to RF and cryoballoon catheters for PVI. This novel system is comprised of a non- steerable catheter with a compliant (9-35 mm diameter) balloon at the tip[380] (figure 8). The catheter is introduced into the LA via a transeptal puncture by femoral vein access. The transeptal sheath has a 15 French outer diameter. The system was originally designed necessitating two operators, one to navigate the balloon to the PV ostium and the other to guide laser application and recently redesigned for a single operator use. The balloon is inflated with a solution of radiopaque "heavy water" (deuterium oxide). Occlusion of the vein permits direct visualization of the PV antrum via a novel 2 French fiberoptic endoscope. A 980 nm diode laser is housed in the central lumen of the catheter. Laser application is performed in a point-by-point fashion around the pulmonary vein. The CardiofocusTM catheter has no electrodes therefore a second mapping catheter is required to check for vein isolation.



Figure 8: CardioFocus Heart Light Laser Balloon[381].

The first human study using endoscopic laser technology was performed in 2009[382]. In the initial experience of 30 patients, 91% of PV's were successfully isolated, and the drug free freedom from AF rate was 60% at 12 months[382]. One episode each of tamponade, stroke, and phrenic nerve paralysis were noted[382]. The first generation system employed a non-compliant balloon and a large laser arc[382]. In the second-generation device, the balloon was made compliant and the laser arc decreased to 30 degrees[337, 383]. Safety and efficacy profile of the second-generation endoscopic laser system was assessed: in 30 patients, 98% complete PVI was achieved with a total

procedural time of 250 ± 62 minutes and a mean fluoroscopy time of 30 ± 18 minutes[383]. Of note, 4 patients (15%) showed esophageal ulceration post procedure[383]. In addition, 1 case of tamponade and 1 case of phrenic nerve paralysis was noted[383]. The most recent worldwide experience of the endoscopic laser balloon was reported on 406 patients from 16 centers[384]. The acute PVI rate was 98% with 79% isolated on the first visually guided attempt. At 12 months, 60% of patients remained in sinus rhythm[384]. Recently, different energy levels during endoscopic ablation was compered and found that higher energies were associated with a higher rate of achieving PVI without an increased risk of complications[385]. The ability to achieve PVI with the endoscopic laser balloon versus the cryoballoon was assessed in a prospective study of 144 patients[386]. At 12 months, recurrence of AF occurred in 37% of patients in the cryoballoon group and 27% in the laser group (p = 0.18)[386].

Other energy sources, such as high intensity focused ultrasound (HIFU) and microwave are available and studied but aren't widely used in catheter ablation.

High-intensity focused ultrasound (HIFU) is one of several approaches available for PVI (figure 9). The first ablation using this technology in humans was reported in 2000[195]. Ultrasound (US) is a form of vibration energy that can cause thermal tissue injury[387]. The vibration

wave propagates and creates mechanical movement of particles within a medium, which is then converted to heat[387]. Thus, tissue damage is due to thermal injury and further tissue damage also results from the acoustic cavitation, a process of micro-bubbles formation by the propagated US wave [387]. The lesion created by HIFU were deep and wide (up to 11 mm) [388] (figure 10). The first generation HIFU balloon was a non-steerable over-the-wire device [387]. The energy delivered was circumferential around the balloon equator [387]. The success rate was only 40% due to large or funnel-shaped PV ostium and early branching[389]. The success rate at 1 year with this approach was 75% with 2 patients (13%) had permanent phrenic nerve palsy despite the verification of the absence of phrenic nerve capture as reported in a cohort of 15 patients[390]. The second-generation balloon was developed with a steerable catheter and a forward projection focused US beam to be more suitable for antral PVI to avoid PV stenosis and PNI[391]. Technically[387, 392], a double transeptal puncture is required, including 16.5F sheath for the HIFU catheter. A second 8 F sheath for the circular (lasso) catheter is positioned inside the PV. Additional electrodes are positioned at the discretion of the operator but usually include at least a decapolar catheter in the coronary sinus (CS). Different sizes of HIFU, including diameters of 24, 27, and 32 mm, balloons are available. HIFU application time varies between 40 and 90 seconds and depends on the balloon size (40, 60, and 90 seconds for balloon size of 24, 27, and 32 mm, respectively). Epicardial AF ablation during surgical AF ablation procedures is now available using Epicor ablation system (St Jude Medical, Minneapolis, MN, USA) with a 2-year freedom from AF of 81% for PAF and 56% for PsAF[393]. Overall, HIFU technique carries a high complication rate, however the utility of this approach should be developed further due to its potential for extracorporal and epicardial ablation.



Figure 9: High-intensity focused ultrasound HIFU catheter with the inflated balloon[394].



Figure 10: Lesion formation with high-intensity focused ultrasound HIFU is shown in a model of a canine heart. (A) A deep, septal lesion is shown. Arrow denotes the deepness of the HIFU lesion. (B) A discrete necrotic lesion is shown with sparing of the surrounding tissue. RV, right ventricle; LV, left ventricle[395].

Microwave (MW) ablation is an option for PAF treatment. It is typically carried out in patients undergoing concomitant open-heart surgery, including mitral valve replacement or repair. A microwave probe is used to create lines of conduction block by thermal damage without causing charring 'coagulum' [396] (figure 11) rather than the incisions created in the traditional Cox maze surgery (multiple strategically

placed incisions are sutured and a 'maze' of scar tissue subsequently forms at incision site that create lines of electrical blocks, success rate of \approx 90%)[397]. The main outcome has been studied in a randomized controlled trail in 43 patients: open-heat surgery and microwave ablation (24 patients) versus open-heart surgery only (19 patients), showed 92% of patients in the surgery-microwave ablation were in SR compared with 32% of patients in the surgery alone group (p < 0.05)[398]. At 12 months 67% (12/18) of patients in the surgery-microwave group were in SR compared with 33% (3/9) of surgery alone group (p < 0.5)[398]. The microwave ablation is performed with concomitant cardiac surgery, it was difficult to evaluate microwave ablation complications. The main complication reported was in-hospital mortality and the requirement for permanent pacemaker. In-hospital mortality in the previous randomized trial was 4.2% (1/24) for patients having surgery microwave ablation compared with 5.3 (1/19) for patients treated with surgery only[398].



Figure 11: Surgical ablation catheters A: unipolar multielectrode surgical probe with a malleable shaft, with 7 10 mm coil electrodes with 3 mm spacing. B: continuous microwave probe with 4 mm antenna[399].

Ablation technologies and catheter types

Advances in catheter designs and technologies for AF ablation are evolving continuously. Most of AF ablation use single point RF energy catheters. A point-by-point approach using single RF ablation is associated with a number of limitations, including that of a long procedure time. To achieve better lesion quality, higher success rate and lower complications rate, circular ablation catheters were designed and developed, such as balloon and multi-electrode are catheters now available to overcome ablation procedures complexity, limitations and challenges.

Balloon-based ablation systems, balloon technologies aimed on eliminating PV-trigger especially at early stages of PAF. The balloon system offers a method in performing electric isolation with minimum number of lesions. Three different balloon based technologies focused on PV ostia ablation: cryoablation, HIFU and laser[400]. Each of these ablation technologies has different potential benefits. HIFU offer a transmural ablation without the complete occlusion of the vein that is required with other technologies[401]. Laser therapy can be combined with endoscopic visualization and cryoablation have less risk of esophageal injury or ablation-induced perforation[402]. Initially, balloon-based technique displayed limited success due to their inability to ablate non-PV sites (other LA substrates for non-PAF) and the technical anatomical challenges that was associated with RPV isolations (especially, right inferior pulmonary vein (RIPV)). Additionally, these systems

sometimes are not adaptable to anatomic PV variability. Therefore, these limitations certainly add to cost (when additionally using conventional catheter for non-PV sites) and complexity of the procedure. However, these techniques have comparable success rates with RF ablation for PVI and shorter procedure time[352, 375, 403, 404].

Multi-electrode ablation catheters are another technology for simultaneous delivery of multiple ablation lesions during RF application. Early multi-electrode design includes the MESH® catheter (Bard Electrophysiology, MA, USA) (figure 12) and the Pulmonary Vein Ablation Catheter® (PVAC) (Medtronic Ablation Frontiers, CA, USA) (figure 13). The MESH catheter is an expandable non-steerable circular catheter with 36 electrodes [400]. The PVAC is a circular deflectable catheter with 10 poles capable of delivering RF energy in unipolar and bipolar modes[400]. One of the major limitations of these catheter designs is the lack of irrigation[405]. Open irrigation to cool the catheter allows more energy to be delivered without limitation of catheter overheating. Therefore, in an attempt to overcome this limitation, the nMARQTM Catheter (Biosense Webster, CA, USA) (figure 13), which is an irrigated multipolar catheter, has been developed and introduced. Studies are ongoing to determine long term outcomes following ablation with the nMARQ catheter[403]. In addition to their role in PV isolation, multielectrode catheters were developed for substrate-based ablation in the LA. The Tip-Versatile Ablation Catheter (TVAC, Medtronic Ablation Frontiers, CA, USA) was designed to create simultaneous linear lesions in the LA, e.g. roof lines, mitral isthmus line and cavotricuspid isthmus lines (CTI) [406]. The TVAC was previously reported to have comparable outcome to conventional ablation for CTI with reduced procedure

time[406]. There are currently no randomized studies comparing conventional ablation with TVAC for roof and mitral lines.



Figure 12: Multi-electrode catheter (Mesh Mapper–Ablator, Bard Electrophysiology). The upper panels show electrode array (top left), fully expanded to allow contact with the atrial endocardium (top right). The lower panels show fluoroscopic images (lower left, right anterior oblique view; lower right, left anterior oblique view) with the catheter array deployed in the left atrium and expanded fully to make circular contact with the atrial wall[407].


Figure 13: Pulmonary Vein Ablation Catheter (Gold) delivering phased RF (left) [408] and nMARQ(right)[409].

Force-sensing technologies, the force applied to the tissue during RF ablation affects the size and safety of the lesion and is measured by grams. An average contact force (CF > 20 g was associated with higher long-term ablation success and < 10 g was associated with unstable catheter contact and reduced 12 months patient outcome[410]. One of the most important recent developments in AF ablation is the design of catheters that provide an assessment on catheter-tissue contact during ablation to ensure transmurality and stability. These catheters have sensors integrated into the tip, which provide real-time information on contact. A number of studies have convincingly demonstrated

that catheter contact force correlates with the delivery of effective ablation lesions and durable PVI[410-412]. Further, clinical outcomes were reported to be superior in patients undergoing AF ablation with contact force catheters as compared with conventional ablation catheters[413]. The two main contact force catheters currently in use for AF ablation are the ThermoCool© SmartTOUCH[™] catheter (Biosense Webster, CA, USA) and the TactiCath[™] catheter (Endosense, Inc., Geneva, Switzerland) (figure 14).



Figure 14: ThermoCool SmartTouch catheter[414] (left) and TaciCath catheter(right) [415].

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Chapter 2

OBJECTIVES

Circular catheter in paroxysmal AF

Circular catheter in persistent AF

Atrial scar on MRI and pulmonary vein reconnection

OBJECTIVE 1

A randomized comparison of circular versus single point-by-point pulmonary vein isolation

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Abstract

Introduction

Point-by-point standard ablation using single-tip (conventional) catheter is the main current technique for pulmonary vein isolation (PVI) but it can be challenging. A circular, multi-electrode, mapping and ablation catheter (nMARQ) may provide faster PVI.

Methods

We designed a randomized comparison between circular versus conventional PVI with the primary end point of reconnection: acutely, in the index procedure, and at 3 months, at the time of a repeat procedure.

Results

Eighty-one patients randomized to circular (nMARQ n = 38) versus conventional (Thermocool Navistar n = 43) underwent PVI for paroxysmal atrial fibrillation. Both groups had similar characteristics: nMARQ age 61 ± 11 years (84% male) and TC age 60 ± 9 years (68% male). NMARQ procedures were shorter (RF and procedure duration), with fewer RIPV reconnections, both acutely and at 3 months (index: 1 (3%) versus 7 (16%), p = 0.044, redo: 21(18%) versus 36 (28%), p = 0.05). Patients ablated with the circular catheter also had shorter repeat procedures

suggesting more discrete PV reconnections (nMRAQ: 142 \pm 56 versus TC: 186 \pm 76 minutes, p = 0.001). At 12 months follow up, 77% of patients in nMARQ group and 79% in TC group were in SR (p = 0.852). No major procedural complications were observed.

Conclusion

This randomized study shows that nMARQ catheter is 3 times faster in isolating the PVs, with shorter RF and procedure time. It is also associated with fewer PV reconnections at 3 months. NMARQ appeared to be safe with no major procedural complications.

Introduction

Electrical pulmonary vein isolation (PVI) by catheter ablation, to eliminate trigger activity or to alter arrhythmogenic substrate, is the mainstay of treatment for patients with symptomatic and drug refractory paroxysmal atrial fibrillation (PAF)[416].

However, atrial fibrillation (AF) recurrence after PVI is common (20-55%)[135, 417-420] and generates significant extra costs, including repeat hospital admissions and repeat procedures. PV electrical reconnection is considered the dominant mechanism of recurrence [226] that limits long-term success and remains a current issue despite advances in catheter design, ablation techniques and AF treatment strategies. Other potential mechanisms of late recurrence have been described, due to electrical and structural atrial remodeling as a result of aging, heart failure, inflammation, diabetes, obesity [417, 421, 422].

Recent catheter technologies such as catheter localization, catheter stability and contact force monitoring might be associated with better and more durable radiofrequency (RF) lesions at first attempt.

Point-by-point standard ablation using single-tip (conventional) catheter is the main current technique for PVI but it can be challenging, complex and time-consuming. A circular, multi-electrode, mapping and ablation catheter (nMARQ) was developed, which provides fast and

effective PVI with comparable success and safety [423]. To the best of our knowledge, the circular ablation catheter has not been compared to the conventional point-by-point approach in a randomized study of PVI. Moreover, the acute and late reconnection rate using circular catheter versus point-by-point ablation remains unknown. We designed such a randomized comparison with the primary end point of reconnection rate: acutely, in an index procedure, and at 3 months, in a repeat procedure.

Methods

Study population

Patients ≥ 18 years, suffering from symptomatic, drug refractory PAF (self-terminating episodes of < 7 days), as defined by ACC/AHA/ESC (American College of Cardiology/ American Heart Association/ European Society of Cardiology) guidelines[419] were eligible to participate in the study. Exclusion criteria were: left atrial (LA) thrombus, severe mitral valvulopathy, class III/IV NYHA (New York Heart Association) heart failure, oral anticoagulation contraindication, redo-ablation, untreated psychiatric disorders and pregnancy. Patients were provided with written informed consent and were affiliated to or recipients of a social welfare regimen. The study was approved by the Institutional Clinical Research and Ethics Committee.

Index ablation procedure

All patients were anticoagulated for at least 1 month before the procedure. Oral vitamin K anticoagulation was uninterrupted for the procedure. LA thrombus was excluded either by transoesophageal echocardiography (TEE) or cardiac computerized tomography (CCT) < 5 days prior to the procedure. Antiarrhythmic drugs (AADs), excepting amiodarone, were discontinued for \geq 5 half-lives before the procedure.

Conscious sedation was achieved with intravenous midazolam (0.2 mg/kg), morphine sulphate (0.1 mg/kg to 0.2 mg/kg) and, if necessary, sufentanil (by 5μ g up to 20μ g) with continuous non-invasive vital sign monitoring. Surface electrocardiograms (ECG) and bipolar endocardial ECG were continuously displayed and recorded at a sweep speed of 100 mm/s and filtered from 0.05 to 100 Hz and 30 to 250 Hz, respectively (LabsystemProTM EP recording system, Boston Scientific BSCI, MA, USA).

Using bupivacaine hydrochloride local anesthesia (100 mg/20 ml subcutaneous SC), three femoral vein sheaths were inserted (8 F, 7 F and 6 F) for vascular access. A steerable quadripolar catheter (Xtrem Sorin, France or Dynamic, Boston scientific, Marlborough, MA, USA) was positioned inside the coronary sinus (CS) through the 6F sheath. A single transeptal puncture (TSP) was obtained using a 98 cm BRK needle (St. Jude Medical) inserted through a long sheath (Agilis, St. Jude Medical) for patients randomized to nMARQ. For those randomized to point-by-point ablation, the transeptal puncture was carried out using a 78 cm BRK needle and a SLO long sheath (St. Jude Medical). Access

to the LA was confirmed by pressure monitoring and contrast injection (Lobitridol 300 mg l/mL) under fluoroscopy. The long sheath was continuously perfused with heparinized saline (2500 U for 500 ml) at 200 mL/h to reduce the risk of thrombus formation. Immediately after TSP and guide wire insertion, a bolus of intravenous heparin (0.5-0.8 mg/kg) was injected. Heparin was monitored throughout the procedure every 20 to 30 minutes by activated clotting time (ACT) with a target of 300-400 seconds.

According to treatment group, either a circular (nMARQ[®], Biosense Webster) or a conventional (NAVISTAR[®] THERMOCOOL[®], Biosense Webster) catheter was used for mapping and ablation. When the nMARQ catheter was used, it was inserted through the long sheath.

In the conventional group, a mapping circular catheter (Lasso®, Biosense Webster) catheter was introduced through the long sheath (described below).

Mapping and ablation

LA and PV anatomy were then reconstructed using fast anatomical mapping (FAM) with nMARQ or Lasso catheter (according to randomization) connected to the Carto® 3 Navigation System (Biosense Webster, Diamond Bar).

The nMARQ catheter [423] has 10 open irrigated electrodes used for both mapping and ablation (electrode length 3.5 mm, spacing 4 mm, maximum catheter diameter 8.4 F) arranged on an adaptable circle (diameter 20-35 mm), to allow optimal positioning in the PV antrum (figure 1 and 2). The catheter was irrigated at 60 mL/min 0.9 saline during RF delivery (CoolFlow, Biosense Webster). The generator (nMARQ Generator, Biosense Webster) delivers RF energy through the 10 separated electrodes in uni- or bipolar mode. Maximum power used was 25 Watt (20 W for posterior wall to reduce the risk of oesophageal injury), temperature 45 °C, maximum duration time 60 seconds in unipolar mode). Catheter position, placement and contact was monitored and optimized before any RF application. Contact was assessed visually with fluoroscopy and also by impedance-based technology provided by Carto® 3 (Tissue Connect, Biosense Webster). RF parameters were continuously monitored during ablation and intermittent fluoroscopy was obtained to assess diaphragm movement, in order to prevent right phrenic nerve injury during right PV ablation. For confirmation of PV isolation, the circular catheter was moved slightly more distally before and after ablation (using the smallest diameter) to verify far-field signals and assess for entrance block. Pacing for phrenic nerve capture and oesophageal temperature monitoring were not routinely used.

Navistar Thermocool (TC) is an open loop, irrigated deflectable, single electrode mapping and ablation catheter (3.5 mm tip and 3 ring electrodes, catheter diameter 7.5 F). Catheter irrigation was delivered by a pump (baseline 2 mL/min, 8-15 mL/min during energy delivery, 0.9% saline via CoolFlow®, Biosense Webster). RF parameters were: power 30 W (25 W on the posterior wall), max temperature 52 °C, RF

duration time 30-60 seconds. With the ablation catheter, we used a 10-pole circular catheter, (Lasso) for PV mapping. PVI was achieved by creating a wide antral line around ipsilateral PVs combining point-by-point and dragging ablation techniques depending on operator preference. The ablation of the inter-vein area was optional, (figure 3). Targeting the earliest PV potential activation approximately 5 to 10 mm from PV ostium was sometimes performed to target a residual gap and complete the isolation.

RF duration, in minutes, was evaluated and compared in 3 ways: each vein separately: right superior PV (RSPV), right inferior PV (RIPV), left superior PV (LSPV) and left inferior PV (LIPV); ipsilateral pulmonary vein pairs, RPV and LPV; and all PVs together.

PV electrical disconnection was confirmed by lasso catheter and pacing for entrance block, exit block, and reconfirmed systematically after 30 minutes with adenosine injection (in absence of contraindication) (figure 4). Cavotricuspid isthmus (CTI) ablation was performed for patients with documented typical atrial flutter in both groups and LA defragmentation ± direct current cardioversion (DC) shock/AADs were allowed if AF persisted after PVI.

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Redo procedure at 3 months

Patients were systematically offered a second procedure irrespective of symptoms or recurrence to evaluate PV for electrical reconnection using conventional strategy. No nMARQ catheters were used in repeat procedures.

The procedure was performed as for the index procedure with conventional catheters. LA and PV 3D anatomy were reconstructed and highdensity anatomical mapping was acquired with Carto 3 system using TC and/or Lasso NAV. Each PV antral region was carefully evaluated for isolation or electrical reconnections/gaps in PV line using Lasso mapping catheter. PVs were divided into 4 segments (superior, anterior, inferior and posterior) and each segment with reconnection was targeted with RF ablation (TC) until complete PVI was achieved (figure 5). PVI was confirmed locally by the Lasso catheter, with pacing for entrance and exit block and adenosine as explained in index procedure.

The CTI line if present was rechecked for bidirectional block and re-ablated again if necessary. Additional LA defragmentation ± DC shock/AADs were allowed if AF persisted after PVI.

Clinical follow up, recurrence and complications

Following ablation, patients continued oral anticoagulation and were advised to continue AADs for 1 to 3 months to control transient tachyarrhythmia episodes during the blanking period. Out-patient clinical follow up (FU) evaluation for symptoms and 24 h Holter monitoring was performed systematically at 3, 6, and 12 months after the procedure. At 1 month, patients were evaluated for PV stenosis by contrast-enhanced magnetic resonance imaging (MRI).

Complications related to the procedures were recorded to respect local regulatory requirements for safety and diligence.

End points

The study primary end point was to compare the efficacy of circular versus conventional ablation catheters for PVI in patients with PAF and to assess reconnection rate: acutely, in the index procedure; and at 3 months, at the repeat procedure. Secondary end point was to assess clinical recurrence 3 months, 6 months and 12 months in both groups.

Statistical Analysis

Continuous variables were expressed as mean ± SD. Categorical data were expressed as counts and percentages. Continuous variables were compared using Student t tests or the non-parametric Mann-Whitney U test as appropriate. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. All univariate predictors with p-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (SPSS, Inc.,) and Prism version 5.00 (GraphPad Software).

Results

Study population

Eighty-one patients with symptomatic, drug refractory paroxysmal AF were enrolled in the study and referred for PVI. Thirty-eight patients were randomly assigned to PV ablation with the nMARQ catheter and 43 patients to PV ablation with the TC catheter. The majority of patients were at low clinical cardiovascular profile risk (CHA2DS2-VASc < 2), mild structural heart disease and normal or near normal left ventricular ejection fraction (LVEF) (Table 1).

Index ablation procedure

At baseline, 8 patients (21%) in nMARQ group and 8 patients (19%) in TC group were in AF. Complete PVI was achieved successfully in both groups (100%), with no cross over.

• Radiofrequency duration for PVI (table 2)

RF duration was significantly shorter in nMARQ group, either vein-by-vein or when comparing ipsilateral veins or all 4 veins (p < 0.001). Isolation of the LIPV required a shorter RF duration compared to the other PVs in both groups.

• Adenosine and acute PV reconnection rates after complete PVI

Thirty minutes after PVI, adenosine challenge was performed in 34 (92%) and 38 (88%) patients in the nMARQ and TC groups respectively.

A lower reconnection rate in RIPV in nMARQ group was observed, compared to TC (Table 3), 3% versus 16\%, p = 0.044). RSPV in nMARQ group and LSPV in TC group had a higher reconnection rate when compared to other veins of the same catheter group.

The acute reconnection rate per PV segment was available in 11 (73%) patients in the nMARQ arm and 17 (74%) patients in the TC arm as shown in table 1 in supplementary files. The reconnection rate in the anterior segment of RSPV was significantly lower in TC compared to nMARQ group 12% versus 46% respectively, p = 0.044). The latter had the highest reconnection rate compared to other PV segments in nMARQ group. On the other hand, the inferior segment of RIPV and the anterior segment of LSPV (24%) had the highest reconnection rate in TC group.

There was no significant difference in the number of acute reconnection per patients between both groups (Table 4). Seventy percent of patients had no acute reconnection in nMARQ versus 58% in TC group. In some cases, PV reconnection was limited to one vein (22% with nMARQ versus 30% with TC). The total number of acutely reconnected PV was higher in the TC group but this was not statistically significant (p = 0.351).

• Additional interventions

Table 5 shows the rate of LA defragmentation, CTI ablation for documented atrial flutter, total non-PV RF duration, DC, and AADs (Flecainide) used to restore SR after PVI in both groups.

There was no significant statistical difference between both groups in non-PV ablations and DC/AADs. RF duration for non-PV ablation was significantly lower in nMARQ group compared to TC (5 ± 3 versus 15 ± 11 min, p = 0.014), respectively.

• Procedural parameters

Total procedure duration was 111 \pm 35 versus 202 \pm 52 minutes (P < 0.001, total RF duration was 14 \pm 6 versus 43 \pm 14 minutes (p < 0.001) and X-ray exposure was 26 \pm 11 versus 46 \pm 27 minutes (p < 0.001) in nMARQ versus TC, respectively.

Follow-up (redo) procedure

Symptomatic recurrence was observed in 17/37 (46%) and 16/43 (37%) in the nMARQ and TC groups, respectively (Table 7).

Of 81 patients, 62 accepted a repeat procedure at 3 months, 30 patients had PVI previously with nMARQ catheter and 32 patients with TC catheter. At baseline, 2 patients were in AF in nMARQ (7%) and TC (6%) group.

• PV reconnection rate at 3 months

The total reconnection rate was significantly lower in the nMARQ group compared to the TC group (15% versus 20%, p = 0.049). The RIPV was the most challenging vein, with the highest reconnection rate compared to other veins in both groups and a significantly lower reconnection rate in the nMARQ group compared to the TC group (18% versus 28%, p = 0.05), respectively, as shown in table 6.

• Radiofrequency duration in PV

RF duration at repeat procedure was not significantly different between groups as shown in table 2 in the supplementary file. RPV RF duration was 8 ± 5 minutes; LPV RF duration was 7 ± 8 minutes in nMARQ and 10 ± 6, 10 ± 7 minutes in the TC group.

• Repeat procedure parameters

Total procedure time was significantly lower in patients initially treated with nMARQ (142 \pm 56 min versus 186 \pm 76, p = 0.001), respectively. Total RF (16 \pm 13 versus 23 \pm 16, P = 0.072) and X-ray exposure (35 \pm 25 min versus 48 \pm 32, p = 0.084), were shorter in nMARQ versus TC respectively, but not significantly.

Clinical Follow up

The success rate at 1 year was 77 % of patients in nMARQ group and 79 % in TC group. AF recurrence (symptomatic and by Holter monitor) at 3, 6 and 12 months are shown in table 7. At 12 months, data was available for both groups in 73 patients in whom 15 patients (21%) had still AF. Eight patients had PAF and 7 PsAF (2 of these patients had valvular heart disease).

• Safety outcomes, adverse events and complications

Major adverse events occurred in 2 patients (3%), LIPV stenosis with LSPV thrombosis 2 months after redo procedure in a patient from the TC group, and renal infarction due to embolism 8 months after repeat ablation due to AF recurrence in nMARQ group. The patient who had LIPV stenosis with LSPV thrombosis (1 year after redo ablation) received a LIPV angioplasty with bare metal stent (BMS) Cook 8 mm X 20 mm.

Two patients (3%) had puncture-related complications after repeat procedures, including 1 arteriovenous fistula and 1 femoral artery aneurysm. One (1%) patient had an acute pericardial effusion in nMARQ group during the index procedure. He was percutaneously drained with no consequences. There were no incidences of stroke, phrenic nerve paralysis or esophageal fistula.

Discussion

Major findings of this study:

- This randomized study demonstrates that the nMARQ catheter is 3 times faster in isolating PVs, while preserving efficacy. This circular ablation catheter demonstrated shorter RF time in all veins, shorter procedure duration and less x-ray exposure, compared to conventional catheter in the index procedure.
- In index procedures, additional ablation at non-PV sites (when needed) was faster with the nMARQ catheter.
- Our study benefited from a high acceptance rate for systematic PV assessment at 3 months. It allowed to demonstrate fewer PV reconnections at 3 months in the nMARQ group.
- RIPV reconnection was less common after ablation with the nMARQ catheter, both acutely and at 3 months.
- Patients ablated with the circular catheter also had shorter repeat procedures suggesting more discrete PV reconnections.
- The circular ablation catheter appeared to be safe with no major procedural complications.

PV reconnections, acutely and at 3 months

Our results are in line with several studies which have demonstrated that PVI using nMARQ is feasible and acutely successful in 96 to 100% [423-427].

The RF duration to isolate the veins has been reported to vary from 10 to 14 minutes [423, 424], with procedure time from 86 to 131 minutes [423-425, 428] and X ray exposure from 4 to 26 minutes [287, 423-425, 428].

Acute reconnection has been reported in 22% (Lasso only) to 42% when adenosine was used [423, 425].

Our findings confirm that, when using the nMARQ catheter, the RSPV is the most challenging vein, requiring more RF applications and with a higher acute reconnection rate per vein and per segment; particularly at the anterior segment. On the other hand, RIPV showed a significantly lower reconnection rate per vein in nMARQ acutely and at 3 months, particularly at the posterior segment when compared to TC.

Our study shows heterogeneous efficacy of the nMARQ catheter, with superiority on the RIPV, particularly on the posterior segment, and at the ridge between LAA and LSPV. This may reflect better catheter stability and contact. This observation may guide improvements in performance on other veins and segments. In a large, multicenter study, 374 patients underwent PVI with nMARQ for PAF and persistent AF (PsAF) in 5 centers with an acute PVI rate of 99.6%. Again, RF times were longer in the superior veins compared to the inferior veins (LSPV 4 ± 3 , RSPV 4 ± 2 , LIPV and RIPV 3 ± 2 min, p = 0.0001). And the anterior aspect of RSPV lesion was also identified as a weak point using this catheter.

PV reconduction is the dominant finding at repeat procedures for AF recurrence, and has been observed in 94% of patients after point-bypoint ablation[417]; which may reflect areas of poor catheter contact and lesion discontinuity.

Different "one shot" catheter designs and technologies aiming at reducing procedure and fluoroscopy time for PVI have been considered and tested over the last decade. In our study, procedure time to achieve PVI with nMARQ was 111 \pm 35 minutes, with fluoroscopy of 26 \pm 11 minutes. In a meta-analysis of 23 cryoablation studies, the mean procedure time was 206 \pm 72 minutes, with fluoroscopy of 46 \pm 13 minutes[429]. In another meta-analysis of 42 studies of AF ablation with PVAC catheter, average procedure time were reported as 117 \pm 33 minutes, with fluoroscopy of 27 \pm 10 minutes.[430].

Safety and complications

Several recent studies have reported on outcomes and complication rates following ablation with the nMARQ catheter 287, 423-427, 431, 432]. Of 894 patients included in 8 studies, major complications were observed in 6 patients (0.7%) including 4 deaths following nMARQ ablation. Three patients died from oesophago-pericardial fistula [287, 424] and 1 had fatal sepsis from an unknown source [424]. The mortality rate with the nMARQ catheter seems higher than the 0.1% reported with conventional catheters [293]. However, it is important to highlight that the latter involved a larger population (> 30,000 patients) and was a registry based on physician willingness to declare complications. Oesophageal lesions detected by endoscopy were attributed to the use of higher RF power in the posterior wall[426] and prolonged RF duration delivery [287]. In our study, no major complications or mortalities were identified with nMARQ catheter except for one acute cardiac tamponade during the initial procedure 1/38. However, pulmonary vein stenosis (TC group) and renal embolism (nMARQ group) due to AF recurrence occurred after redo procedures with the conventional catheter. However, we didn't use oesophageal temperature monitoring or systematically perform post ablation endoscopic evaluation to document thermal oesophageal damages. Studies in larger cohorts of patients are necessary to define the mortality rate associated with nMARQ ablation.

Serious safety concerns regarding silent cerebral lesions (SCL) caused by multi-electrode ablation in the LA have arisen recently[433, 434]. Scaglione[425] reported no major procedural complications and no SCI by 24 hours post procedural cerebral diffusion-weighted DW-MRI, in contrast with the results reported by Deneke[426] which showed that 14 out of 43 patients (33%) had SCL following nMARQ ablation. We did not routinely acquire cerebral imaging post ablation.

The complication rate in cryoablation reported in a systematic review was relatively low with 6% incidence of phrenic nerve palsy (PNP), most of them being transient[429]. In a systematic review of PVAC ablation, the overall procedural complication rate appeared to be low (acute procedural complications were 2%, though non-uniform screening may limit the accuracy of this estimate). However, high rates of silent cerebral ischemic lesions (38%-45%) have been reported, significantly higher than with irrigated RF (7%-17%) or cryoablation (4%-6%) [430].

Long-term outcome

A single procedure 1-year success rate of 65% has been reported using nMARQ [424], similar to the 67% reported in a meta-analysis on conventional RF catheters [435]. Success rate after single and repeat procedures was 66 and 77% respectively, similar to the success rates reported in conventional RF and multi-electrode ablation and higher than in cryoablation[436, 437].

Another single operator study reported 83% success rate at 1 year with the nMARQ[287]. In our study, 77% of patients in nMARQ group and 79% in TC group were in SR (p = 0.852) at 1 year. Long-term success (\approx 18 months) with freedom from AF, AFL or AT was 80% in a study comparing nMARQ to TC Smart Touch in 86 patients with PAF and PsAF with no significant difference in both groups (p = 0.78)[428].

Limitations

Our study is a single center randomized study that did not meet the planned enrolment target. The catheter withdrawal from the market in June 2015 interrupted patient recruitment to the study. However, the patient cohort recruited has been sufficiently large to demonstrate statistically significant results.

We did not routinely monitor oesophageal temperature during ablation or perform post ablation esophageal endoscopy or cerebral imaging (MRI). However, we did not observe any oesophageal or cerebral complications, possibly as a consequence of reduced power and duration of RF delivery in the posterior LA.

Another potential limitation was in the technology used in conventional single electrode catheters. We used an impedance-based method rather than direct measurements of force sensing technologies 'contact force' that associated with a more complete ablation.

Our observation of nMARQ efficacy and safety suggests that this catheter may be a promising alternative to conventional point-by-point AF ablation and the knowledge gained using this catheter should be used to build better ablation tools in the future.

Conclusion

This randomized study shows that the nMARQ circular irrigated catheter is 3 times faster in isolating the PVs, with shorter RF and procedure time. It is also associated with fewer PV reconnections at 3 months. This catheter appeared to be safe with no major procedural complications in this study.

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Disclosure

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Table 1: Baseline patient characteristics

N=81	nMARQ (n 38)	Navistar TC (n 43)	р
Male Sex, n (%)	32 (84)	29 (68)	0.081
Age, mean ± SD (years)	61 ± 11	60 ± 9	0.613
BMI ¹ , mean ± SD (kg/m ²)	25.5 ± 3.8	26.8 ± 3.8	0.118
Hypertension, n (%)	8 (21)	13 (30)	0.347
Diabetes Mellitus, n (%)	1 (3)	1(2)	0.929
Embolic events, n (%)	3 (8)	5 (12)	0.574
Structural heart disease, n (%)			0.555
Ischemic heart disease	4 (11)	1(2)	0.126
Dilated or hypertrophic cardiomyopathy	2 (5)	1(2)	0.484
Valvular heart disease	5 (13)	6 (14)	0.917
Echocardiographic parameters			

¹ BMI, body mass index

Left ventricular ejection fraction, mean ±	62 + 6	61 + 6	0 221
SD (%)	05 ± 0	01±0	0.231
Left atrial surface area,	18 0 + 5 0		0 6 0 7
mean ± SD (cm ²)	10.9 ± 5.0	19.5 ± 5.0	0.00/
AF ² related parameters			
AF history, mean ± SD (months)	71 ± 77	89 ± 86	0.352
AF max duration episodes,			0 6 5 7
mean ± SD (hours)	23.0 ± 20.9	27.3 ± 30.7	0.05/
AF at baseline, n (%)	8 (21)	8 (19)	0.782
≥ 1 DC ³ shock, n (%)	4 (10)	6 (14)	0.743
AADs ⁴ used before AF ablation,	2((25)	(1)	
n (%)	30 (95)	41 (95)	1.0
Amiodarone use before AF ablation, n (%)	18 (47)	16 (37)	0.485

² Atrial Fibrillation

³ DC, direct current cardioversion
 ⁴ AAD, antiarrhythmic drug

CHA2DS2-VASc, mean ± SD	1 ± 1	1 ± 1	0.388

Table 2: RF¹ duration in index procedure

min ± SD	nMARQ (n 38)	Navistar TC (n 43)	р
RSPV ²	4 ± 3	11 ± 8	<0.001
RIPV ³	3 ± 2	11 ± 5	<0.001
LSPV ⁴	3 ± 2	12 ± 6	<0.001
LIPV ⁵	2 ± 2	8 ± 5	<0.001
RPV ⁶	6 ± 4	20 ± 9	<0.001
LPV ⁷	5 ± 3	18 ± 8	<0.001
Total PV	12 ± 5	38 ± 13	<0.001

 ¹ Radiofrequency
 ² Right superior pulmonary vein
 ³ Right inferior pulmonary vein
 ⁴ Left superior pulmonary vein
 ⁵ Left inferior pulmonary vein
 ⁶ Right pulmonary veins
 ⁷ Left pulmonary veins

n (%)	nMARQ (n 34)	Navistar TC (n 38)	р
RSPV	7 (19)	4 (9)	0.213
RIPV	1(3)	7 (16)	0.044
LSPV	5 (14)	9 (21)	0.384
LIPV	2 (5)	3 (7)	0.772
Total reconnection rate	15 (41)	23 (53)	0.270
RF duration, mean (min) ± SD	2 ± 1	4 ± 3	0.078

Table 3: Acute PV¹ reconnection rate per patient in index procedure

¹ Pulmonary vein

n (%)	nMARQ (n 37)	Navistar TC (n 43)	р
0	26 (70)	25 (58)	0.351
1	8 (22)	13 (30)	0.450
2	2 (5)	5 (12)	0.442
3	1 (3)	0	0.463
4	0	0	1.0
Total reconnection rate	11 (30)	18 (42)	0.351

Table 4: Number of acute PV reconnection per patient in 4 PV in index procedure

Table 5: Non-PV ablation/cardioversion in index procedure

	nMARQ (n 37)	Navistar TC (n 43)	р
LA defragmentation, n (%)	8 (22)	5 (12)	0.226
CTI, n (%)	10 (27)	6 (14)	0.145
RF duration, mean (min) ± SD	5 ± 3	15 ± 11	0.014
DC, n (%)	2 (5)	8 (19)	0.075
Flecainide, n (%)	2 (5)	6 (14)	0.203

Table 6: Reconnected PV segments in repeated procedure

n (%)	nMARQ	Navistar TC	р
RSPV	17/120 (14)	23/128 (19)	0.416
RIPV	21/120 (18)	36/128 (28)	0.051
LSPV	19/120 (16)	27/128 (21)	0.287
LIPV	15/120 (13)	15/128 (12)	1.0
All Veins	72 /480(15)	101/512 (20)	0.049

Table 7: Follow-up

3 months n (%)	nMARQ (n 37)	Navistar TC (n 43)	р
Symptoms	17 (46)	16 (37)	0.429
Holter +	18 (49)	15 (35)	0.212
6 months	nMARQ (n 32)	Navistar TC (n 39)	р
Symptoms	5 (16)	9 (23)	0.432
Holter +	5 (16)	6 (15)	0.978
12 months	nMARQ (n 35)	Navistar TC (n 38)	Р
Symptoms	10 (29)	12 (32)	0.780
Holter +	8 (23)	8 (21)	0.852

Supplementary files:

n (%)		pMARO (p. 11)	Navistar TC (n	n
			17)	Ρ
RSPV	Superior	0 (0)	0(0)	-
	Anterior	5 (46)	2 (12)	0.044
	Inferior	1 (9)	2 (12)	0.823
	Posterior	1 (9)	1(6)	0.747
RIPV	Superior	0(0)	3 (18)	0.140
	Anterior	o (o)	3 (18)	0.140
	Inferior	o (o)	4 (24)	0.082
	Posterior	1 (9)	2 (12)	0.823
LSPV	Superior	1 (9)	2 (12)	0.823
	Anterior	3 (27)	4 (24)	0.823
	Inferior	1 (9)	2 (12)	0.823

Table 1: Reconnection rate per PV segment in index procedure

	Posterior	0 (0)	0(0)	-
LIPV	Superior	1 (9)	1(6)	0.747
	Anterior	1 (9)	1(6)	0.747
	Inferior	1 (9)	1(6)	0.747
	Posterior	1 (9)	1(6)	0.747

Table 2: RF duration in repeated procedure:

min ± SD	nMARQ (n 25)	Navistar TC (n 28)	р
RSPV	7 ± 5	6 ± 5	0.744
RIPV	7 ± 5	6 ± 5	0.843
LSPV	7 ± 7	9 ± 5	0.619
LIPV	5 ± 6	5 ± 4	0.791
RPV	8 ± 5	10 ± 6	0.239
LPV	7 ± 8	10 ± 7	0.308

Table 3: Reconnection rate per PV segment in repeated procedure¹

¹ Per PV segment, RIPV posterior segment and LSPV anterior segment showed lower reconnection rate in nMARQ compared to TC (13% versus 34%, p = 0.053 and 10% versus 41% p = 0.006), respectively. Among all veins segments for each group, the RIPV inferior segment in both groups and the LSPV anterior segment in TC group only had higher reconnection rates.

()			Navistar TC (n		
n (%)		nMARQ (n 30)	32)	р	
RSPV	Superior	5 (17)	5 (17)	1.000	
	Anterior	3 (10)	6 (20)	0.279	
	Inferior	5 (17)	3 (10)	0.448	
	Posterior	4 (13)	9 (30)	0.117	
RIPV	Superior	3 (10)	3 (9)	0.933	
	Anterior	6 (20)	9 (28)	0.455	
	Inferior	8 (27)	13 (41)	0.246	
	Posterior	4 (13)	11 (34)	0.053	
LSPV	Superior	7 (23)	6 (19)	0.658	
	Anterior	3 (10)	13 (41)	0.006	
	Inferior	3 (10)	2 (6)	0.588	
	Posterior	6 (20)	6 (19)	0.901	
LIPV	Superior	4 (13)	3 (9)	0.622	

Anterior	2 (7)	3 (9)	0.696
Inferior	5 (17)	4 (13)	0.642
Posterior	4 (13)	5 (16)	0.798

n/16 (%)	nMARQ (n 30)	Navistar TC (n 32)	р
0	5 (17)	4 (13)	0.728
1	5 (17)	3 (9)	0.467
2	8 (27)	8 (25)	1.0
3	5 (17)	7 (22)	0.751
4	4 (13)	3 (9)	0.703
5	-	1 (3)	1.0
6	1 (3)	2 (6)	1.0
7	2 (7)	1 (3)	0.607
8	-	2 (6)	0.492
9	-	1 (3)	1.0

Table 4: Number of PV segment reconnection rate per patient in repeated procedure¹

¹ Per patient, no statistically significant difference was observed between groups. Zero reconnection was found in 17% versus 13% of patients in nMARQ and TC groups, respectively. The majority of patients in both groups had reconnection in two segments per vein. Nine/16 reconnected PV segments was the maximum number of reconnections. Total PV reconnection extent was 2 ± 2 segments versus 3 ± 2 segments in the nMARQ and TC groups, respectively (p = 0.177).

Total PV segment reconnection	25 (83)	27 (87)	0.728
Total PV segment			
reconnection extent, n ±	2 ± 2	3 ± 2	0.177
SD			

Table 5: Non-PV ablation/cardioversion in repeated procedure

	nMARQ (n 30)	Navistar TC (n 35)	р
LA defragmentation, n (%)	5 (17)	11 (31)	0.168
CTI, n (%)	8 (27)	12 (34)	0.507
RF duration, mean (min) ±	22 ± 14	20 ±16	0.818
SD	·		
DC, n (%)	1(3)	2 (6)	0.648

Table 6: Patients on AADs at 12 months

n (%)	nMARQ (n 38)	Navistar TC (n 43)	р
On AADS @ 12 months	18 (45)	20 (44)	ns ²
Flecainide	4 (10)	5 (11)	ns
Amiodarone	1 (3)	1 (2)	ns
Beta blockers	16 (40)	17 (38)	ns
Ca ²⁺ channel blockers	1 (3)	2 (4)	ns
Propafenone	0 (0)	1 (2)	ns

² Non significant



Figure 1: (A) disconnection of PV potentials (red circles) after 4 seconds in SR by nMARQ ablation catheter in the RSPV (shown by blue arrow). (B) AP x-ray view showing nMARQ catheter position in RSPV and quadripolar catheter ablation position in the CS. ECG, surface electrocardiogram. PV, pulmonary vein. RSPV, right superior pulmonary vein. SR, sinus rhythm. CS, coronary sinus. AP anteroposterior.



Figure 2: Left atrial 3D geometrical mapping in AP and PA view displaying the location of ablation lesions in PV using nMARQ catheter in index procedure. AP, anteroposterior. PA postero-anterior.



Figure 3: Left atrial 3D geometrical mapping in AP and PA view displaying the location of ablation lesions in PV using Thermocool catheter in index procedure. AP, anteroposterior. PA posteroanterior.



Figure 4: (A) PV potential (second signal component in red circles, first signal component is atrial far-fields) recovery after 30 minutes of adenosine injection. PV disconnection is shown by yellow line. (B) AP x-ray view showing Lasso mapping catheter position in LSPV and quadripolar catheter ablation position in the LIPV to assess reconnection in LPV after adenosine injection. ECG, surface electrocardiogram. PV, pulmonary vein. LSPV, left superior pulmonary vein. LIPV, left inferior pulmonary vein. SR, sinus rhythm. AP anteroposterior.

OBJECTIVE 2

Persistent atrial fibrillation ablation using circular irrigated ablation catheter

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Under thesis director revision

Abstract

Introduction

Persistent atrial fibrillation (PsAF) ablation remains time consuming, even when guided by non-invasive mapping. We investigated the role of a multielectrode irrigated circular catheter for PsAF ablation.

Methods:

A circular ablation catheter (nMARQ[®], Biosense Webster, Inc) with 10 irrigated simultaneous mapping and ablation electrodes was used in 50 PsAF patients (age 60 ± 11 years, left atrial size 21.8 ± 9.7 cm^2 and AF maximum duration 10.6 ± 9.3 months). Ablation was guided by non-invasive mapping (ECUVETM, Cardioinsight Inc.) in 32 patients (64%). Pulmonary vein isolation (PVI) was systematically performed.

Results:

After targeting additional non-PV regions including 3 ± 2 indicated by ECVUE (1-6), AF terminated in 37 patients (74%), into atrial tachycardia (AT) in 22 and directly to sinus rhythm (SR) in 15 patients). Thirteen patients were in SR during the procedure. PVI required 8.01 \pm 5.27 minutes of RF. Eleven patients required direct current (DC) shock to terminate AF. Linear lesions were performed for AT: 14 LA roof lines, 13 mitral isthmus lines and 27 cavotricuspid isthmus (CTI). Using total of 20.24 \pm 17.25 minutes of RF. Interestingly, 5/8 roof line block, 4/5 mitral isthmus

line block and 19/24 CTI line block were blocked with nMARQ catheter only 5.08 ± 4.58 , 3.30 ± 2.56 and 3.26 ± 2.12 minutes of RF, respectively. A conventional ablation catheter was required to complete linear lesions and obtain the block in 3 roof lines, 1 mitral isthmus line and 5 CTI. Mean procedure duration was 3.18 ± 1.03 hours. Complications included 1 pericardia effusion managed conservatively and 1 transient ischemic (TIA) resolved without any neurological sequelae. One year follow up data was available in 38 patients (76%), 18 patients (66%) were in SR and 13 patients (34%) had AF recurrence in whom 2 patients (15%) had AT recurrence.

Conclusion

Circular ablation catheter demonstrated encouraging results for rapid, safe and effective PsAF ablation when guided by non-invasive phase mapping. The catheter can be used for linear ablations and CTI in addition to PVI, thus obviating the need for an additional ablation catheter in the majority of patients.

Introduction

Catheter ablation for persistent atrial fibrillation (PsAF) remains time consuming due to issues such as undue radiofrequency (RF) application, long procedural duration and post-procedural atrial tachycardia (AT) [438]. Different ablation techniques and strategies were available to treat PsAF and improve clinical outcomes, including pulmonary vein isolation (PVI) only [80, 205], ganglionated plexi ablation[210], linear lesions in the left atrium (LA)[229], complex fractionated atrial electrogram (CFAE)-based ablation[266], stepwise approach[275] and driver based ablation[78, 439, 440].

Pulmonary vein isolation role in PsAF is debated but likely to be limited because of the additional involvement of LA substrate (fibrosis) maintaining AF due to extensive electrical and anatomical remodeling[159].

A new technology for AF analysis using commercially available non-invasive body surface mapping (ECVUE[™] Cardioinsight Technologies) was available to identify multiple atrial wavelets, macro-reentries and localized sources (focal or re-entry/rotor), which played an important role in driving and maintaining AF[159, 164, 165]. This technique images electrograms used to generate isochrones maps[441]. An ablation strategy guided by non-invasive phase mapping has been reported to be effective in catheter ablation of PsAF[159].

The circular, irrigated multi-electrode catheter (nMARQ®) was introduced and developed for simultaneous mapping and ablation, and demonstrated high success rate and short procedure time for paroxysmal and persistent AF ablation[287, 423, 424, 428]. Previous studies in nMARQ safety and efficacy suggested that further research was needed to clarify long-term outcome[287, 424, 426]. Nevertheless, the occurrence of oesophageal fistulas with fatal outcome in some studies was of major concern[287, 424, 426]. Therefore, the catheter was recalled from the market in June 2015 for further investigation[442]. However, the knowledge gained using this catheter should be used to build better ablation tools in the future.

The aim of this study was to investigate the role of nMARQ catheter in PsAF ablation and evaluate 1-year outcome.

Methods

Study design

A circular mapping and ablation catheter (nMARQ) with 10 irrigated electrodes was used in PsAF patients. PVI ablation was systematically performed. Additional ablations for non-PV sites was guided either by CARTO® (CFAE based ablation) with or without additional noninvasive mapping ECVUE[™] Cardioinsight (driver based ablation). Procedure end point was AF termination to sinus rhythm (SR) or to atrial tachycardia (AT). In case of AF termination to AT, further mapping and ablation was performed accordingly. Linear lesions (roof and/or mitral isthmus

lines) were performed for AT only. Cavotricuspid isthmus (CTI) line was performed in presence of typical flutter history or pervious CTI line that was no longer blocked. A conventional ablation catheter was occasionally required to complete linear lesions and obtain complete block. Follow-up data was collected at 3, 6, 12 months to assess success and recurrence rates.

This study aimed to evaluate safety and efficacy of the circular catheter combined with noninvasive mapping technologies in PsAF patients, and to investigate and assess the role/efficacy and the safety of the catheter in non-PV/ linear lesions and success rates at 3, 6 and 12 months.

Study population

Inclusion criteria were: PsAF, refractory to at least 1 antiarrhythmic drugs (AADs), and of duration > 7 days[443]. Exclusion criteria included the presence of LA thrombus, sub-therapeutic or contraindication to anticoagulation, significant valvular heart disease, and New York Heart Association (NYHA) class III or IV heart failure. Written informed consent was obtained from all patients. The study was approved by the ethic committee.

Non-invasive body surface mapping-guided ablation (ECVUE[™] Cardioinsight Technologies[™])

Signal acquisition from the patient and subsequent computational methods used in the reconstruction of non-invasive maps using multiple torso electrodes have been described previously [158, 159, 441]. Briefly, a 252-electrode vest was applied to the patient's torso and connected

to the non-invasive imaging system, and surface potentials were recorded [158]. It was followed by a non-contrast thoracic CT scan acquiring 64 section multi-detector [159] to obtain high-resolution images of the heart and the vest electrodes [158]. The 3D epicardial bicameral atria geometries were reconstructed from segmental CT images [158]. The relative positions of body surface electrodes was visualized on the torso geometry[158]. The system reconstructed epicardial potentials, unipolar electrograms and activation maps from torso potentials during each beat/cycle using mathematical reconstruction algorithms. Details of the mathematical methods were provided in previous publications[161-163, 444, 445]. For the purpose of this study, AF electrograms were acquired during a long ventricular pause – spontaneous or diltiazem-induced [159]. AF maps were created using specific algorithms combining wavelet transform and phase mapping applied to the reconstructed epicardial potentials [159]. Activation maps were computed using traditional unipolar electrogram intrinsic deflection based (dV/dT) max method[159]. AF drivers were classified into two categories: (i) focal activation with centrifugal propagation from a point and (ii) re-entry/rotor demonstrating rotated wave with full-phase propagation around a functional or anatomical center point[159]. The core and trajectory of re-entrant drivers and focal sources were depicted on the patient-specific biatrial geometry [446, 447]. The number of foci and re-entry through the total duration of all AF windows were displayed on cumulative driver-density maps [159]. The order of ablation was determined based on the cumulative driver map [159]. After acquiring atrial geometry on 3D electoanatominal mapping system (CARTO® 3, Biosense Webster Inc), the region having the highest density of re-entrant drivers was targeted first followed by the region with the secondhighest driver density and so on[159]. Within the driver area, rapid and continuous fragmented signals and the activation gradient between proximal and distal electrodes were preferentially targeted for ablation[275] (figure 1).

The endpoint of RF application was PVI with nMARQ catheter, elimination of fragmented potential and slowing of the AF cycle length at the local site[159]. Each RF application targets dominant clusters of AF driver at 25 Watt (W) (Max 20 W in the posterior wall) using the nMARQ catheter with temperature cut-off set at 45 °C[159]. If AF persists after ablation of the first targeted region, the second-highest density area of driver was subsequently ablated in the same way[159]. Non-PV sites were ablated using nMARQ catheter or with conventional catheter as needed. Unipolar ablation with power delivery of 25 W was performed at all non-PV sites (Max 20 W for posterior wall).

The endpoint of the procedure was AF termination to sinus rhythm (SR), atrial tachycardia (AT) or completion of RF applications targeting all driver areas[159]. PV isolation was systematically performed. Re-entrant drivers were preferred target versus focal drivers as they have previously been shown to be strongly associated with AF termination[447]. Importantly, drivers with good quality signals on the non-invasive map were considered as priority targets regardless of their type[159]. If AF persisted after driver-based ablation and PVI, it was terminated by electrical cardioversion[159].



Figure 1: A. Phase mapping demonstrating a posterior view of the left atrium (LA) in persistent AF patient. Rotors (green and turquoise color) are located on the inferolateral LA as well as adjacent to the right pulmonary veins. The rotors adjacent to the right pulmonary vein are stable. Those at the inferolateral aspect of the LA are more unstable. The line in peach color indicates the trajectory of an unstable rotor. B. Radiographic image of nMARQ catheter on the posterior wall adjacent to the right pulmonary vein targeting multiple rotors.

Invasive mapping (Carto® 3 system) and ablation procedure

PVI using the nMARQ catheter and generator has previously been described[423]. Briefly, all patients were on anticoagulation therapy for at least 4 weeks before procedure. After femoral access, a decapolar catheter (Xtrem, Sorin) was positioned in the coronary sinus (CS). Access into the LA was obtained by transeptal puncture (TS) under fluoroscopic and pressure guidance (98 cm BRK needle, Agilis sheath,
St. Jude Medical, St. Paul, MN, USA; Direx sheath, Bard, Lowell, MA, USA). Following transeptal puncture, activated clotting time (ACT) was maintained at > 300 seconds using heparin boluses. The sheath was continuously perfused with heparinized saline at 200 mL/h.

Three-dimensional (3D) LA geometry was created using circular, open-irrigated catheter nMARQ catheter (Biosense Webster, Irwindale, CA USA) and the Carto® 3 mapping system (Biosense Webster, INC. Diamond Bar, CA, USA)[424]. All patients underwent PVI using nMARQ. In cases where AF terminated to AT or Flutter (FL), activation map and additional ablation to target the sources using either circular or single tip irrigated (Navistar TC SF Biosense Webster, Irwindale, CA, USA) ablation catheter were performed.

Post-procedural management and follow-up

Post-procedural oral anticoagulation and antiarrhythmic drugs (AADs) were continued for 3 months and thereafter according to individual CHADS VASc risk scores. Treatment with proton pump inhibitors (PPI) was prescribed for 2 weeks in all patients. In case of AF recurrence, cardioversion was recommended to restore sinus rhythm.

Follow-up (FU) at 3 moths, 6 months and 12 months was collected. Recurrence of AF defined as any AT lasting > 30 seconds on an ECG loop recorder or ECG. Procedure-related major adverse events (embolic complications, phrenic nerve damage, vascular complications, PV stenosis and death) were recorded in all patients.

Statistics

Continuous variables were expressed as mean ± SD. Categorical data were expressed as counts and percentages. Continuous variables were compared using Student *t* tests or the non-parametric Mann-Whitney U test as appropriate. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. All univariate predictors with p-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (SPSS, Inc.,) and Prism version 5.00 (GraphPad Software).

Results

Clinical Characteristics

A total of 50 patients with symptomatic, drug-refractory, PsAF were included in the study. They were predominantly male (90%), aged 60 \pm 10.5 years. Left ventricular ejection fraction (LVEF) was 49.2 \pm 22.6%. Left atrial surface area and volume were 21.8 \pm 9.7 cm², 68.5 \pm 47.7 ml respectively. Clinical characteristics are summarized in table 1.

Table 1: Clinical characteristics

Baseline patient characteristics	N = 50
Age, mean ± SD (years)	60 ± 10.5
AF diagnosis time, mean ± SD (months)	49 ± 71.1
AF maximum duration time mean ± SD	10.6 ± 9.3
(months)	
DC for AF, n (%)	39 (78)
CAHDS VASC ≥ 2, n (%)	20 (40)
Diabetes mellitus (DM), n (%)	8 (16)
Hypertension (HTN), n (%)	16 (32)
Coronary artery disease (CAD), n (%)	4 (8)
Dilated/hypertrophic cardiomyopathy	10 (20)
(DCM/HCM), n (%)	
Congenital heart disease (CHD), n (%)	1(2)
Valvulopathy, n (%)	16 (32)
1	

Cerebrovascular accidents, n (%)	4 (8)
Paroxysmal nocturnal dyspnea (PND), n	5 (10)
(%)	
Left ventricular ejection fraction (LVEF),	49.2 ± 22.6
mean ± SD	
Left atrial surface area, mean ± SD	21.8 ± 9.7
LA volume, mean ± SD	68.5 ± 47.7
Total number of AADs, mean ± SD	2 ± 0.9
1 AADs	21 (43.8)
2 AADs	17 (35.4)
3 AADs	7 (14.6)
4 AADs	2 (4.2)
Amiodarone, mean ± SD	30 (60)

Procedural Details

Of the 50 patients with PsAF treated using the nMARQ catheter, 32 patients (64%) underwent ablation guided by non-invasive mapping $(\text{ECVUE}^{TM}, \text{Cardioinsight Inc.})$. Thirty-seven (74%) presented in AF while the arrhythmia was induced in 13 patients (26%). PVI was performed in 47 patients (94%) using 8.01 ± 5.27 minutes of RF. RF time in RPV was 4.45 ± 2.47 minutes and LPV 4.36 ± 2.40 minutes. A conventional ablation catheter was required in 16 patients (33%), to treat non-PV substrate sites in 7 patients and linear lesions in 9 patients.

A total number of 46 patients (92%) had ablation for non-PV sites (CFAE based or driver based) with an additional RF time of 17.24 \pm 12.42 minutes. At least 1 linear ablation was performed for AT in a total of 19 patients (38%) (Roof n = 14, Mitral isthmus n = 13). Roof line only was done in 6 patients, mitral line only was done in 5 patients and both lines (roof and mitral isthmus) were done in 8 patients. Roof line block was obtained in 8/14 patients (57%) in whom 5 patients had block with nMARQ catheter only and 3 patients had a backup block ablation with conventional catheter. Total RF time for roof line was 6.34 \pm 4.58 minutes and RF time for roof line with nMARQ ablation only was 5.08 \pm 4.07 minutes. Mitral isthmus line block was obtained in 5/13 patients (39%) in whom 4 patients had block with nMARQ catheter and 1 patient had block with conventional catheter. Total RF time for mitral isthmus line was 9.50 \pm 9.24 minutes and RF time for mitral isthmus line with nMARQ ablation only was 3.30 \pm 2.56 minutes. Cavotricuspid isthmus (CTI) line was performed in 27 patients (54%) resulting in complete

block in 24 patients (89%) of whom 19 had block using the nMARQ catheter only. Total RF time for CTI line was 4.40 ± 3.43 minutes and RF time for CTI ablation with nMARQ ablation only was 3.26 ± 2.12 minutes.

AF was terminated in 37 (74%) patients, in 15 patients (31%) into SR (sinus rhythm), into AT terminated by ablation in 12 patients (25%) and into AT terminated by direct-current (DC) shock in 10 patients (20%). In patients in whom RF ablation failed to terminate AF, DC shock was used in 11 (22%) and AADs injection in 1 patient (2%). AADs were used in combination with DC shocks in 10 (20%).

The total procedural RF time was 31.13 ± 17.31 minutes, total procedure time was 3.18 ± 1.03 hours and X-ray duration was 45.53 ± 22.46 minutes.

• Non-invasive mapping-guided ablation

Non-invasive mapping-guided ablation was applied in 32 patients (64%). After targeting 3 ± 2 additional non-PV sites as indicated by ECVUE (1-6), PVI was performed in 30 patients (93%), non-PV sites were ablated in 31 patients (97%) and linear ablations were performed in 9 patients (28%). RF time for PVI was 8 ± 5.27 minutes (RPV RF was 4 ± 3.03 minutes and LPV RF was 4.21 ± 2.59 minutes), RF time for non-PV sites was

14.54 ± 10.3 minutes. Use of an additional conventional ablation catheter was required in 12 patients (38%) for backup ablation in 6 patients for non-PV sites ablation and in 6 patients for linear ablation.

Roof line was ablated in 5 patients, mitral isthmus line was ablated in 7 and both lines were ablated in 3 patients. Roof block was obtained in 2/5 patients (40%) of whom 1 patients had block with the nMARQ catheter only and 1 patient required additional RF using a conventional catheter touchup. Total RF time for roof line was 0.58 ± 2.40 minutes and with nMARQ only ablation was 4.00 minutes. Mitral isthmus block was obtained in 2/7 patients (29%) of whom 1 had block with the nMARQ catheter and 1 required additional RF using a conventional catheter for touchup. Total RF time for mitral line was 2.58 ± 7.39 minutes and with nMARQ only was 6.0 minutes. CTI ablation was performed in 15 patients (47%) resulting in complete block in 13 patients (87%) of whom 8 patients had block with the nMARQ catheter only and 5 required additional RF using a conventional catheter. Total RF time for the CTI line was 2.40 ± 4.07 minutes and for nMARQ ablation only was 3.07 ± 0.154 minutes.

AF was terminated in 25 patients (78%), into SR in 9 patients (28%), AT terminated by ablation in 9 patients (28%), AT terminated by DC shock in 7 patients (22%). In patients in whom RF ablation failed to terminate AF, DC shock was used in 6 (19%) and AADs in 1 (3%). Total RF ablation was 29.44 ± 15.43 minutes, procedure time was 3.35 ± 0.57 hours and x-ray was 47.51 ± 25.54 minutes.

Safety Outcomes

Of the 50 patients who underwent ablation with nMARQ catheter ± non-invasive mapping-guided ablation for PsAF, 2 patients (4%) (neither of whom received non-invasive mapping guided ablation) had steam pop with nMARQ catheter on CTI (25 W, total RF duration 5 minutes) and on superior vena cava (SVC) (25 W, total RF duration 30 seconds), with no adverse consequences and 1 patient (2%) had a transient ischemic stroke (aphasia) resolved without neurological sequelae.

Short and long-term outcome

Follow-up data was collected at 3, 6 and 12 months. Details are shown in Table (2).

Table 2: Follow up data at 3, 6, and 12 months

N (%)	SR	AF	AT
3 months n= 24 (48)	12 (50)	7 (29)	5 (21)
6 months n= 22 (44)	12 (55)	6 (27)	4 (18)
12 months n= 38 (76)	18 (66)	11 (29)	2 (5)

Re-ablation was performed in 9 patients, 5 patients and 5 Patients at 3, 6 and 12 months.

At 12 months, 38 patients (76%) follow up data were available, 18 patients (66%) were in SR and 13 patients (34%) had recurrence, in whom 11 patients had AF and 2 patients had AT. Five patients (13%) underwent a fourth ablation procedure, 3 (8%) were treated with AADs and 5 patient's data was not available.

Discussion

This study reports efficacy, safety and 1 year outcome using nMARQ circular, multielectrode, irrigated ablation catheter for PsAF. In most patients in this series, the procedure was guided by non-invasive mapping (ECVUE[™] Cardioinsight Technologies). This study demonstrates that the combination can be used safely and allows a long-term efficacy of 66% in the entire patients and 65% when guided by non-invasive mapping. The nMARQ catheter proved interesting versatility in this study, being successfully used to target non-PV regions hosting rotors in 100% of cases. Linear ablation could also be completed by nMARQ catheter, particularly at CTI, but also for roof line.

Efficacy

NMARQ efficacy in PsAF ablation was associated with 52-96% success rate and short ablation time as reported in previous studies and was comparable to our study [287, 424, 427]. Moreover, the study demonstrated that nMARQ catheter was feasible in non-PV sites ablation,

including CFAE or driver-based ablation and linear ablation (roof block with nMARQ was 62% (RF duration was 5.08 ± 4.07 minutes), mitral isthmus block with nMARQ was 80% (RF duration was 3.30 ± 2.56 minutes) and in CTI was 79% (RF duration was 3.07 ± 01.54 minutes), in addition to achieving successful PVI (94%). Non-PV sites ablation with nMARQ alone reported to be effective in blocking CTI and roof lines with limited number of RF application (6.0 ± 4.9 minutes, 4.8 ± 2.9 minutes, respectively) without the need for additional ablation with conventional catheter, however, the study is a cohort multi-center study had small number of PsAF patients underwent non-PV ablation (30/111 patients (27%) including linear ablations[424]. The nMARQ catheter was also effective for simultaneously targeting multiple left and right atrial sites with high-frequency fractionated signals[424].

The procedure time for PsAF with PVI only was 75 minutes[287] and PVI with additional non-PV sites ablation was 144 minutes[424]. We reported 180 minutes including non-invasive phase mapping time. In the non-randomized study comparing nMARQ to smart touch, procedural time was similar regardless of the catheter used (smart touch 115 \pm 17 minutes versus nMARQ 125 \pm 24 minutes, p = 0.200)[427].

Safety

In 50 patients, 1 patient (2%) had transient ischemic stroke (aphasia) resolved without sequelae. Incidence of ablation-related asymptomatic cerebral events (ACE) in previous studies varies between 2% and 41% [448-457]. The platinum-tipped PVAC catheter, Medtronic Inc., Carlsbad,

CA USA) was associated with highest rates of ablation-related ACE due to non-irrigated radiofrequency ablation, which increased the risk of thrombus formation. In a meta-analysis neurological embolic complications have previously been reported with multielectrode ablation catheter technologies such as the PVAC catheter (Medtronic Inc.) in 0.63% [458]. The nMARQ ablation system has similarities to the PVAC ablation catheter but the difference is that the nMARQ catheter is continuously irrigated. None of the previous studies on nMARQ outcomes have reported clinical strokes [423, 425, 426, 431, 432]. Nevertheless, a small cohort study identified silent cerebral lesions (SCL) in 14/43 (33%) following nMARQ ablation[426]. The findings emphasize the importance of uninterrupted oral anticoagulation and maintenance of higher activated clotting times during nMARQ ablation. Comparison between PVAC and nMARQ showed that the ablation-related silent cerebral events (SCE) rate is similar between both groups [448-457]. Though a randomized study comparing the incidence of SCE after PVAC, nMARQ and thoracoscopic surgical AF ablation reported higher number of ablation-related SCE in the PVAC: 2 patients (13.3%), 1 patient (6.7%) in nMARQ with one patient that did not resolve at 3 months and no surgical patients with ablation-related ACE.[459]. Of note, the study reported high background prevalence of MRI-detected cerebrovascular disease at baseline that was not ablation related (5.1%) and at 3 months (3.3%)[459]. No major post procedural complications or mortalities occurred such as atrio-oesophageal fistula, pulmonary vein stenosis or phrenic nerve palsy (PNP).

Long-term outcome

The outcomes of nMARQ ablation at 1 year were comparable to conventional ablation[424]. In a meta-analysis of 6 studies reporting outcomes of PsAF ablation with conventional catheters, 1-year success rates were 52% [460]. In the multi-center cohort study of nMARQ catheter for PsAF, 65% of patients were free from AF at 1 year[424], although these results should be interpreted with caution because of significant heterogeneity in the ablation strategy, the additional use of conventional ablation to nMARQ and the small number of patients (18%) in the follow-up data as previously mentioned. In the largest single-center series where PVI only was treated with PsAF ablation, 6 months success rate was 52% [287]. The present identified a success rate of 55% and 66% arrhythmia free at 6 months and 12 months in the available data of 44% and 76% patients, respectively.

Limitations

The study was a single center study. We did not routinely monitor esophageal temperature during ablation or perform post ablation esophageal endoscopy or cerebral imaging (MRI) to rule out esophageal injury and cerebral lesions. However, we did not observe any esophageal or cerebral complication related to the circular catheter. Follow-up data were only available in 76% of patients.

Conclusions

The circular multielectrode irrigated mapping and ablation catheter demonstrates encouraging results for rapid, effective and safe technique in PsAF ablation, especially when guided by non-invasive mapping. The circular catheter was feasible for non-PV CFAE or driver passed ablation and can be used effectively and safely for CTI and linear ablations in addition to PVI. Therefore, obviating the need for an additional ablation catheter in the majority of patients.

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Disclosure

Dr. Nora Al Jefairi has no conflict of interest. Drs. Pierre Jais, Frederic Sacher, Meleze Hocini and Michel Haissaguerre have received lecture fees from Biosense Webster for 10.000 USD annually. Other authors have no disclosures.

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OBJECTIVE 3

RELATIONSHIP BETWEEN ATRILA SCAR ON CARDIAC MAGNETIC RESONANCE AND PULMOBARY VEIN RECONNECTION AFTER CATHETER ABLTION IN PAROXYSMAL ATRIAL FIBRILLATION

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ABSTRACT

Background

Pulmonary vein (PV) reconnection is frequent in patients showing atrial fibrillation (AF) recurrence after PV isolation (PVI). Its detection with cardiac magnetic resonance (CMR) may help predict outcome and guide redo procedures. We assessed the relationship between scar on CMR and PV reconnection after catheter ablation for paroxysmal AF.

Methods and results

Fifty-one patients with paroxysmal AF underwent CMR before PVI using either a conventional single-electrode catheter (N = 28) or a circular multi-electrode catheter (N = 23). At 3 months, a second CMR study was performed, followed by a systematic electrophysiological procedure to look for PV reconnection, regardless of AF recurrence. Pre-ablation fibrosis and post-ablation scar were quantified and mapped from late gadolinium-enhanced CMR. CMR results were compared to the distribution and extent of PV reconnection. CMR and electrophysiological findings were compared between catheter types. 3 months after successful PVI, scar gaps were found in 39 (76%) patients, and 78 (39%) veins. Electrical PV reconnection was detected in 45 (88%) patients, and 99 (50%) veins. The extent of PV reconnection related closely to the number of gaps (R = 0.55, P < 0.001), and to scar burden (R = -0.63, P < 0.001). However, the agreement was only fair for the localization of

PV reconnection (k = 0.37, P < 0.001), scar gaps particularly lacking sensitivity in areas of pre-existing fibrosis. The circular catheter was associated with shorter procedures (P < 0.001), more scar (P = 0.01), less gaps (P = 0.01), and less reconnected veins (P = 0.03).

Conclusions

PV reconnection is extremely frequent after PVI. CMR scar imaging accurately predicts its extent, but poorly predicts its location. Multielectrode circular catheters induce more complete ablation.

Introduction

Since the early description of pulmonary vein triggers responsible for atrial fibrillation (AF) episodes,¹ electrical isolation of the pulmonary veins (PVI) with the use of catheter ablation has emerged as a curative approach to obtain rhythm control, particularly efficient in patients with paroxysmal forms of AF.² However, arrhythmia recurrences are still frequent, and often require redo procedures.³ Electrical reconnection of the PVs is a common finding in patients showing AF recurrence,^{4,5} and is presumably the dominant cause. PV reconnection has been related to incomplete scarring around the PVs, because of either gaps on ablation lines⁶ or incomplete scar transmurality.⁷ The extremely high prevalence of PV reconnection despite successful PVI at the acute stage illustrates the challenge of achieving durable, circumferential and transmural scar around the 4 PVs. To address the issue, several innovations have been proposed, including the use of multi-electrode circular ablation catheters, which may improve lesion continuity, as suggested by animal studies.⁸ However, scar distribution after PVI with circular multi-electrode catheters has not been thoroughly studied in patients. On the other hand, cardiac magnetic resonance (CMR) was shown able to detect and quantify post-ablation scar on the left atrium (LA).⁹⁻¹¹ Unfortunately, its ability to detect functionally relevant scar gaps and guide redo procedures is still a subject of substantial debate.¹²⁻¹⁶ This discrepancy might be due to the fact that imaging and EP characteristics were only studied in small series of patients showing recurrences, which induces potential bias, firstly with respect to the pathophysiological nature of the CMR and EP findings, and secondly because it implies studying patients at variable delays since the index procedure. The aim of this study was to assess the characteristics of PV reconnection and CMR scar after PVI in consecutive patients,

regardless of AF recurrence. A secondary objective was to compare scar and PV reconnection characteristics after PVI between conventional single-electrode ablation catheters and circular multi-electrode ablation catheters.

Methods

Population and study design

From June 2013 to March 2016, we prospectively included non-consecutive patients presenting with drug-refractory paroxysmal AF, referred at the University Hospital of Bordeaux for catheter ablation. We did not include consecutive patients as the protocol was dependent on MRI availability. Paroxysmal AF was defined as self-terminated episodes lasting less than 7 days. Exclusion criteria were: contra-indications to CMR (including implantable defibrillators and pace-makers), LA thrombus (ruled out using systematic computed tomography or trans-esophageal echocardiography), severe mitral valvulopathy, heart failure symptoms > NYHA class II (New-York Heart Association), contraindication to oral anticoagulation, history of catheter ablation or cardiac surgery, age < 18 years, and failure to obtain patient consent. All patients underwent a CMR study at baseline followed by a catheter ablation procedure aiming at PVI. To study the impact of catheters types on scar and reconnection at 3 months, patients were randomized to undergo PVI using circular multi-electrode irrigated catheters (nMARQ®, Biosense Webster, Diamond Bar, CA) or conventional irrigated catheters (NAVISTAR THERMOCOOL®, Biosense Webster, Diamond Bar, CA). At 3 months, all patients underwent another CMR study followed by systematic electrophysiological (EP) procedure to

assess for PV reconnection, irrespective of symptoms or AF recurrence. The relationship between scar on CMR and PV reconnection characteristics was analyzed, and these characteristics were compared between both catheter groups. The study was approved by the Institutional Ethics Committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, approval reference 2012-A01494-39). All patients provided informed consent.

Index AF ablation procedure

All procedures were performed under conscious sedation. All patients were under anticoagulation therapy for a minimum of 1 month at the time of the procedure, and vitamin K antagonists were continued. Antiarrhythmic drugs (AADs) were discontinued for \ge 5 half-lives before the procedure, except for amiodarone. After obtaining femoral access a quadripolar steerable catheter (Xtrem, Lilanova/Sorin, UK or Dynamic, Boston Scientific, Marlbourough, MA) was placed in the coronary sinus. Trans-septal puncture was achieved under fluoroscopic guidance, using either a 78 cm BRK needle inserted through a long sheath (SLO, St Jude Medical) in patients randomized in the conventional catheter group, or a 98 cm BRK needle (St Jude Medical, St Paul, MN) inserted through a steerable sheath (Agilis, St Jude Medical) for patients randomized in the circular catheter group. After trans-septal puncture, a bolus of intravenous heparin (0.5-0.8 mg/Kg) was injected. In addition, the long sheath was continuously perfused with heparinized saline, targeting an activated clotting time of 300-400 seconds.

In the circular catheter group, the circular catheter was used to acquire a LA and PV anatomy using fast anatomical mapping in the Carto 3® navigation system (Biosense Webster). Details on the nMARQ® catheter have been described elsewhere.¹⁷ Briefly, the catheter has 10 irrigated electrodes distributed on a circle whose diameter can be modified from 20 to 35 mm depending on the PV antrum anatomy. We applied irrigation with 0.9% saline at the rate of 60 mL/min during RF delivery. RF energy was delivered for 60s per application, in unipolar mode, with a temperature limited to 45 °C, and applying a maximum power of 25 W (Watt) except for electrodes in contact with the posterior wall (20 W or less). Catheter contact was monitored using both fluoroscopy and dedicated signal processing of impedance measurements (Tissue Connect, Biosense Webster). Acute PV isolation was confirmed using activation mapping with the circular catheter positioned distally within the vein using the smallest catheter diameter. In the conventional catheter group, a dedicated mapping catheter was used (Lasso, Biosense Webster) to acquire LA and PV anatomy and to confirm PV isolation. The NAVISTAR THERMOCOOL® catheter was used for ablation. It is an open loop, deflectable, irrigated and single electrode catheter. We applied 0.9% saline irrigation, and delivered RF during 30-60s applications, with a temperature limited to 52 °C, and a maximum power of 30 W (25 W on the posterior wall). PVI was performed under 3D electroanatomical mapping guidance, using a point-by-point and/or a dragging technique. Acute PV isolation was confirmed using activation mapping with the Lasso catheter. In both groups, successful PVI was confirmed again after 30 min, with challenging by adenosine injection, unless contra-indicated. All dormant conduction unmasked by adenosine were targeted by ablation. In the circular catheter group, a subset of electrodes was selectively activated to deliver RF on the reconnected site only. Additional ablation was performed on cavotricuspid

is thmus in patients with history of typical atrial flutter. In addition, ablation of LA complex fractionated atrial electrograms and direct current cardioversion were allowed if AF persisted after PVI. In the circular catheter group, we could selectively activate the electrode(s) exhibiting CFAE to perform local ablation.

Follow-up EP study

Patients underwent a second procedure at 3 months, regardless of potential symptoms or AF recurrence. No circular catheters were used, all patients being mapped with a Lasso® catheter, and ablated with a conventional NAVISTAR THERMOCOOL® catheter when needed, using Carto 3® navigation system (Biosense Webster). PVI was confirmed by mapping PVs with the Lasso® catheter, using pacing to document entrance and exit block. In case of electrical reconnection, the site of reconnection was characterized using detailed activation mapping, and each segment showing reconnection was targeted by ablation until complete PVI was obtained. To enable comparison with CMR scar maps, the sites of ablation resulting in successful elimination of PV conduction were tagged on the 3D geometry, and these reconnection sites were distributed on a 16-segment PV model (anterior, inferior, posterior, superior for each vein). As in the index procedure, all blocks were challenged by adenosine, unless contra-indicated. Fractionated electrograms on either the LA body or PV antrum were also targeted by ablation. Additional ablation could also be performed on the cavotricuspid isthmus, and direct current cardioversion was allowed if AF persisted.

CMR studies

CMR studies were performed within 3 days prior to each EP procedure. Studies were conducted on a 1.5 Tesla system (MAGNETOM AVANTO®, Siemens Medical Systems, Erlangen, Germany), equipped with a 32-channel cardiac coil. Atrial volume and left ventricular ejection fraction were measured on cine images acquired using a breath-held, ECG-gated steady state free precession pulse sequence in order to acquire a stack of 4-chamber slices covering both atria from roof to bottom (slice thickness 6 mm, temporal resolution 15 ms), and a stack of short axis slices covering the entire LV from base to apex (slice thickness 7mm, temporal resolution 20ms). Atrial late gadolinium enhancement (LGE) acquisition was initiated 17 min after the intravenous injection of 0.2 mmol/Kg gadoterate meglumine (Guerbet, Aulnaysous-bois, France). Imaging was acquired in trans-axial orientation using a 3-dimensional, inversion-recovery-prepared, ECG-gated, respiration-navigated gradient-echo pulse sequence with fat-saturation.¹⁸ Typical imaging parameters were: voxel size 1.25 x 1.25 x 2.5 mm, flip angle 22°, TR/TE 6.1/2.4 ms, inversion time 260 to 320 ms depending on the results of a TI scout scan performed immediately before acquisition, parallel imaging with GRAPPA technique with R = 2, 42 reference lines, acquisition time 5 to 10 min depending on patient's heart and breath rate. In post-ablation CMR studies, a second atrial LGE acquisition was performed in sagittal orientation, initiated immediately after the trans-axial acquisition and with the same parameters except for adjustments of the inversion time.

Image analysis

Atrial and ventricular volumes were measured using the multi-slice method, the pulmonary veins and left appendage being excluded from segmentations. The analysis of pre- and post-ablation LGE images was performed by a single observer with 15 years experience in CMR, using MUSIC Software (IHU Liryc, Université de Bordeaux – Inria Sophia Antipolis, France). Scar and fibrosis segmentations were both performed on trans-axial LGE images. The wall of the left atrium was manually traced. On pre-ablation LGE images, atrial fibrosis was segmented by adaptive thresholding of myocardial voxels as described previously.¹⁸ Fibrosis burden was expressed in % of the LA wall, and categorized according to the UTAH method: stage I = 0-10%, stage II = 10-20%, stage III = 20-30%, and stage IV = over 30%.¹⁹ On post-ablation images, LGE was also segmented using histogram analysis, applying the full width at half maximum method,²⁰ with potential additional refinement of the threshold by the expert in case of inaccurate segmentation. In addition, connectivity thresholding was applied to remove isolated pixels related to image noise, with a threshold set around 5 pixels, depending on image quality. Scar burden was expressed in mL, and additional manual segmentations were performed on volume rendering reconstructions of the segmented scar to separately quantify LA scar burden on right veins (RPVs), left veins (LPVs), and outside PV antrum areas. The quantification of scar burden on CMR is illustrated in Figure 1. To analyze LGE distribution, scar maps were displayed by overlaying the maximum transmural intensities on a 3-dimensional surface mesh of the LA endocardium. A color coding was applied to visualize scar heterogeneity, ranging from 50% (scar threshold) to 70% of the maximum signal intensity. The assessment of scar gaps was performed on these 3D scar maps, gaps being distributed on the same 16-segment PV

model as for EP data. In case of circumferential scar on all segments the vein was considered negative. In case a gap was seen on the 3D map further analysis was performed by reviewing multi-planar reconstructions of the original imaging volume in 2 perpendicular planes aligned along the vein axis, as well as in a stack of images parallel to the ostium. Both the trans-axial and sagittal LGE images could be reformatted, depending on the orientation of the vein. This confirmation on the native imaging set was mandatory to categorize a segment as hosting a gap. The assessment of scar gaps on CMR is illustrated in **Figures 2 and 3**. The prevalence and distribution of scar gaps was compared to PV reconnection on a per-patient basis, per-vein basis, and per-segment basis. The agreement between CMR and EP was categorized as either false positive (gap + / reconnection -), false negative (gap - / reconnection +), true positive (gap + / reconnection +), or true negative (gap - / reconnection -). Pre-ablation CMR images were analyzed on all false positive, false negative, and true positive segments. Both 3D fibrosis maps and 3D multi-planar reconstructions were reviewed, and segments were categorized as either fibrosis positive or fibrosis negative.

Statistical analysis

The Shapiro-Wilk test of normality was used to assess whether quantitative data conformed to the normal distribution. Continuous data are expressed as mean ± standard deviation when following a normal distribution, and as median [interquartile range Q1-Q3] otherwise. Categorical data are expressed as fraction (%). The relationship between continuous variables was assessed using Pearson's correlation

coefficient. Independent continuous variables were compared using independent-sample parametric (unpaired Student's t-test) or nonparametric tests (Mann-Whitney U test) depending on data normality. Dependent continuous variables were compared using paired-sample parametric or non-parametric tests (paired Student's t-test, Wilcoxon signed-rank test) depending on data normality. Independent categorical variables were compared using Chi-square test when expected frequencies were \geq 5, and Fisher's exact test when they were < 5. Dependent categorical variables were compared using the paired-sample McNemar's test. The agreement between scar gaps and CMR and electrical reconnection of PVs was assessed on a per-vein basis, using kappa statistics. All statistical tests were two-tailed. A P value <0.05 was considered to indicate statistical significance. Analyses were performed using NCSS 8 (NCSS Statistical Software, Kaysville,UT, USA).

RESULTS

Population baseline and procedural characteristics

A total of 60 patients agreed to participate in the study, of which 9 were retrospectively excluded, either because they eventually did not show at follow-up CMR and EP study (N = 4), or because CMR data were of poor quality (N = 5). Therefore, 51 patients were studied (age 61 ± 9 years, 24% women). The characteristics of the studied population at baseline and during the index ablation procedure are shown in **Table 1.** The median CHA2DS2-VASc score was 1 [0-2]. The median duration of AF history was 36 [24-96] months. The total number of antiarrhythmic drugs was 1.9 \pm 1.0, and 19 (37%) patients were under amiodarone therapy. Baseline CMR showed a mean atrial volume of 57 \pm 11 mL/m², and a LA fibrosis burden categorized as Utah stage I in 2 (4%), stage II in 38 (75%), stage III in 11 (22%) and stage IV in 0 (0%). At the time of the ablation procedure, 9 (18%) patients were in AF. Circular ablation catheters were used in 23 (45%), and conventional ablation catheters in 28 (55%). Successful PVI was obtained in all patients, and completed by additional PV ablation because of adenosine-induced reconnection in 20 (39%), with no significant difference between catheter types (P = 0.26). Non-PV ablation comprised targeting of complex fractionated atrial electrograms in 7 (14%), and linear ablation on cavotricuspid isthmus in 14 (27%). The total RF duration was 29 \pm 17 min, and the total procedure time was 164 \pm 69 min. An acute procedural complication was observed in one patient from the circular catheter group who presented with epicardial effusion (resolved after drainage).

Follow-up CMR study

All 51 patients underwent CMR at 3 months. Findings on follow-up CMR are shown in **Table 2**. LVEF and LA volume did not differ from preablation measurements (P = 0.66 and P = 0.12, respectively). On LGE images, the burden of scar on PVs was 7.8 ± 2.1mL, and tended to be higher on RPVs than on LPVs, although not significantly (P = 0.07). LA scar outside PV areas was found in 4 (8%), and scar on cavo-tricuspid isthmus in 13 (25%). When analyzing PV antrum regions, scar gaps were found in 39 (76%) of the patients, and 78 (39%) of the veins. The prevalence of gaps was higher on RIPV than on both LSPV (P = 0.03) and LIPV (P = 0.01). The mean extent of gaps per patient was 2.2 ± 2.1 segments. Out of 800 segments analyzed, gaps were found in 113 (14%). When compared to baseline LGE images, only 7/113 (6%) of these segments showed pre-existing fibrosis. Examples of pulmonary veins with and without scar gaps on CMR are shown in **Figure 3**.

Follow-up EP procedure

The characteristics retrieved during the EP procedure performed at 3 months are shown in **Table 3**. At the time of the EP procedure, 3 (6%) patients were in AF. On mapping, PV reconnection was detected in 45 (88%) patients, and 99 (50%) of the veins. The prevalence of reconnection did not differ between veins (P = 0.23). The mean extent of reconnection was 3.3 ± 2.4 segments per patient. Additional ablation was performed in all but one patient (98%), consisting of additional ablation on PVs in 49 (96%), targeting of complex fractionated electrograms in 12 (24%), and linear ablation on cavotricuspid isthmus in 11 (22%). The total RF duration was 18 \pm 16 min, and the total procedure time was 166 \pm 74 min. An acute procedural complication was observed in one patient who presented a femoral pseudo-aneurysm that resolved after 24h of compression.

PV reconnection versus scar burden on CMR

The burden of scar on PVs related closely to the extent of PV reconnection (R = -0.63, P < 0.001), as illustrated in **Figure 4A**. Scar burden on PVs tended to be higher in the 6 patients showing no PV reconnection, as compared to those presenting with at least 1 vein reconnected

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 $(9.1 \pm 2.0 \text{ versus } 7.6 \pm 1.9 \text{mL}, \text{P} = 0.06)$. Regional analysis could not be performed on a vein per vein basis because scar could not be quantified separately on each vein. However, the burden of scar on both RPVs was lower in patients showing reconnection on RPVs ($3.8 \pm 1.0 \text{ versus}$ $4.6 \pm 0.7 \text{mL}, \text{P} = 0.01$), while no such difference was found on LPVs (P = 0.10).

PV reconnection versus scar gaps on CMR

The extent of gaps on CMR related closely to the extent of PV reconnection (R = 0.55, P < 0.001), as illustrated in **Figure 4b**. However, on a vein by vein basis, the agreement between CMR and the EP study was only fair for the localization of PV reconnection (k = 0.37, P < 0.001). Scar gaps on CMR were weak predictors of PV reconnection with a sensitivity of 0.57, a specificity of 0.77, a positive predictive value of 0.72, and a negative predictive value of 0.65. The agreement between scar gaps on CMR and PV reconnection was higher on RPVs (k = 0.46, P < 0.001) than on LPVs (k = 0.22, P = 0.003). When analyzing the errors, the 43 false negative (reconnected veins with no scar gap on CMR) were distributed as follows: 11/51 RSPV, 6/51 RIPV, 12/51 LSPV, 14/47 LIPV. The prevalence of false negative differed between veins, and was higher on LIPV than on RIPV (P = 0.03). In contrast, the 22 false positive (scar gap on CMR without PV reconnection) were evenly distributed between veins (P = 0.34). On a per-segment basis, 98/800 segments were categorized as false negative (reconnected segment with no scar gap on CMR), and 44/800 as false positive (scar gap on CMR without PV reconnection). When compared to baseline LGE images, false negative segments showed a higher rate of pre-existing fibrosis than false positive segments (60/98 versus 3/44, P < 0.001).

Impact of catheter type

The EP and imaging characteristics according to the type of catheter are shown in **Table 4**. Baseline characteristics did not differ between groups, except for a substantially higher rate of women in the conventional catheter group (P = 0.02). During the index ablation procedure, the circular catheter group showed a 3-fold reduction of RF duration, and a 2-fold reduction of procedure time (P < 0.001 for both). On CMR at 3 months, patients from the circular catheter group showed higher amounts of scar on PVs (P = 0.01), less veins with scar gaps (P = 0.04), and a lower extent of scar gaps per patient (P = 0.01). On the follow-up EP study, patients from the circular catheter group showed less veins with reconnection (P = 0.03), as well as shorter RF duration (P = 0.03) and redo procedure time (P = 0.007). **Figure 5** illustrates the distribution of scar after PVI with conventional and circular ablation catheters. Of note, scar burden did not relate to RF duration using either conventional catheters (R = 0.04, P = 0.66) or circular catheters (R = 0.20, P = 0.10).

Patient outcome

At 1-year follow-up 41/51 (80%) patients remained free of AF. The 10 recurrences consisted of paroxysmal AF episodes in 7 and persistent AF in 3. The recurrence rate did not differ between groups (8/28 in the conventional group versus 2/23 in the circular catheter group, P = 0.08). Two delayed complication were observed: one patient from the conventional catheter group showed LSPV thrombosis and LIPV stenosis

requiring angioplasty, and one patient from the circular catheter group presented a thrombo-embolic event (renal infarction 6 months after the redo procedure). No patient died during follow-up.

Discussion

This study is to our knowledge the largest series directly comparing scar distribution on CMR and PV reconnection characteristics, and the first to do so in consecutive patients who underwent PVI for paroxysmal AF, regardless of potential recurrence. It is also the first comparison of scar burden and distribution on CMR between irrigated single electrode and circular multi-electrode catheters. Studying 51 consecutive patients who underwent PVI using either conventional or circular catheters, our results confirm that PV reconnection and scar gaps on CMR are extremely prevalent in unselected patients 3 months after successful PVI. While both the scar burden and the extent of scar gaps on CMR correlate closely to the extent of PV reconnection, the performance of CMR to locate sites of PV reconnection remains limited, predominantly because of missed PV reconnections. CMR sensitivity seems particularly limited on sites showing pre-existing fibrosis. Last, besides dramatic reduction in procedure duration, the use of circular multi-electrode ablation catheters is associated with higher scar burden, fewer scar gaps, and fewer reconnected veins after PVI.

Population and methods

The characteristics of the population studied are consistent with the usual population referred for paroxysmal AF ablation. The index ablation procedure conformed to the current state-of-the-art, except for the use of circular multi-electrode catheters in part of the population. The CMR methods used to characterize pre-ablation fibrosis and post-ablation scarring on the LA are consistent with past studies.^{12,18,19,21} However, we chose to perform absolute quantifications of scar burden expressed in mL while many prior studies have reported measurements of scar surface or scar volume indexed on atrial wall volume.^{22,23} The rationale was to take into account scar thickness and to make scar measurements less dependent on atrial wall segmentation, and our results in terms of scar burden after PVI are consistent with prior reports using the same approach.¹¹ The present study confirms that scar burden after PVI is extremely variable between patients (ranging from 2.8 to 16.7 mL in the present study), despite guite standardized ablation protocols. In addition, poor correlation was found between RF duration and scar burden. These findings confirm that the ability to translate acute ablation lesions into chronic scar is highly patient-dependent. In that prospect, post-ablation CMR might be the only method able to characterize the individual response profile to catheter ablation at the tissue level. The analysis of scar gaps from CMR is similar to the one reported in prior studies,¹¹⁻¹⁴ although more refined and automated approaches have recently been described.²⁴ In order not to rely solely on absolute thresholds, all gaps identified on 3D scar maps were confirmed by visual inspection of native images. In addition, a second LGE dataset was systematically acquired in the sagittal plane, closer to the orientation of the PV ostia. We found scar gaps to be extremely prevalent on CMR after PVI, which is consistent

with past studies.¹⁹ Regarding PV reconnection, prior studies have shown that it is an extremely common finding after PVI, even in patients with no recurrence.^{25,26} Transient blocks have been explained by inflammation and heating that can reduce tissue conductivity and cause conduction blocks in areas of viable myocardium.⁶ In the present study, despite the systematic use of adenosine to unmask dormant conduction and minimize this phenomenon,²⁷ the rate of reconnection remained extremely high.

Relationship between scar gaps on CMR and PV reconnection

Although numerous studies have reported interesting correlations between post-ablation scar on CMR and patient outcome after PVI,^{10,21} very few have directly compared scar distribution and sites of PV reconnection.¹²⁻¹⁶ In addition, these few studies showed conflicting results, with some reporting good correlation and suggesting the use of CMR scar maps to guide redo procedures,¹²⁻¹⁴ while others reported poor correlation.^{15,16} The reason for such discrepancy is unclear. It may be due to the fact that imaging and EP characteristics were only studied in small series of patients showing recurrences which induces potential bias, firstly with respect to the pathophysiological nature of the CMR and EP findings, and secondly because it implies studying patients at variable delays since the index procedure. In the current study CMR and EP characteristics after PVI were systematically compared at 3 months in unselected patients. We found significant but poor correlation between scar gaps on CMR and PV reconnection. CMR particularly lacks sensitivity to predict sites of PV reconnection. Interestingly, this sensitivity issue seems to be partly due to the confounding effect of pre-existing fibrosis. Indeed, very few segments with gaps showed

fibrosis on baseline CMR, while a majority of false negative segments (PV reconnection with no gap on CMR) showed fibrosis. Thus, a major limitation of CMR appears to be its inability to distinguish scar from pre-existing fibrosis. However, a significant number of PV reconnections missed by CMR occurred in segments showing no pre-existing fibrosis. These may be explained by the inability of CMR to characterize scar transmurality, because of insufficient spatial resolution. This explanation is supported by prior reports relating PV reconnection and incomplete scar transmurality on histopathology.⁷ False positive cases (gaps on CMR with no reconnection) were less frequent but not uncommon. This is also consistent with prior histopathological reports showing that PVI may be preserved in the presence of gaps of viable myocardium.⁷ Indeed, besides lesion discontinuity other factors can play a role including the geometry of scar gaps,²⁸ the direction of fibers in the gap area,²⁹ and potential source-sink effects. Overall, although the relationship was stronger on RPVs than on LPVs, the performance of CMR to predict sites of PV reconnection seems insufficient to provide relevant guidance during redo procedures.

Relationship between scar burden and reconnection

In contrast, the global correlations between CMR and PV reconnection characteristics were much higher. The extent of PV reconnection related positively to the number of gaps detected on CMR, and negatively to the burden of scar on PVs. This finding supports the use of post-ablation CMR to predict patient outcome.^{10,21} Indeed, many studies have shown that PV reconnection does not directly imply AF recurrence because other factors might play a role.^{25,26} Firstly, the reconnected vein might not be the one hosting the triggers responsible

for AF episodes. Secondly, even if triggers were present in the vein these may have been directly eliminated by ablation despite incomplete PVI. Thirdly, the conduction block, although incomplete, may be sufficient to render PV triggers less arrhythmogenic. However, all of these scenarios become less probable when PV reconnection is large and/or involving multiple veins. In other words, PV reconnection is so common, even in the absence of AF recurrence, that localizing each site of reconnection with the use of CMR might not be the best strategy, while quantifying the degree of reconnection may be a more appropriate and accessible aim.

Impact of circular multi-electrode ablation catheters

The rationale behind the circular multi-electrode ablation technology is to create more complete circumferential lesions during PVI by delivering RF energy simultaneously from multiple electrodes. These catheters have shown promising clinical results.^{17,30} However, their ability to actually improve lesion circumferentiality remains unknown. Although animal studies using a non-irrigated multipolar catheter (PVAC®; Medtronic Ablation Frontiers, Carlsbad, CA) have produced convincing results,⁸ scar characteristics after PVI using circular multipolar catheters have not been thoroughly studied in patients. Using an irrigated circular decapolar catheter (nMARQ, Biosense Webster), our study shows that the technology can achieve successful PVI in much shorter procedure time as compared to a conventional single-electrode irrigated ablation catheter. More importantly, when analyzing CMR results at 3 months, we found the circular catheter to

produce higher amounts of scar on PVs, less veins with scar gaps, and a lower extent of gaps per patient. The follow-up EP study confirmed that this more thorough lesion set was associated with less reconnected veins. As a consequence, the need for additional ablation during the redo procedure was reduced, with shorter RF duration and procedure time, despite similar catheters in both groups (circular catheters were not used during the follow-up EP study). We acknowledge that the immediate clinical implications of our findings may be limited, knowing that the catheter used in the present study has been recalled due to significant thermocouple issues and to several reports of oesophageal fistulas.³¹ However, our results support future developments of the circular multi-electrode ablation technology, as it may both reduce PVI procedure times and improve efficacy.

Study limitations

The main limitation of this study is its study design inappropriate to evaluate a potential predictive value of CMR and EP findings at 3 months. Indeed, in these patients who agreed to undergo a systematic EP study 3 months after PVI, we obviously performed additional ablation to complete the lesion set anytime necessary, so that patients could potentially benefit from this redo procedure. Given the high prevalence of reconnection, this additional ablation was performed in the vast majority of patients. However, predicting patient outcome was not within the scope of the present study, which focused on analyzing the relationship between scar and PV reconnection. Another potential limitation may be the technology used to assess contact force in the group with conventional single electrode catheters. We used an impedance-based method rather than direct measurements of contact force, which may be associated with a more complete ablation set, as previously reported on CMR.³² Last, we acknowledge that the quantification of scar with the use of CMR still lacks validation, and that there is to our knowledge no automated method that outperforms segmentations by experts, as these remain the gold standard.³³ This significantly limits the implementation of the method in current practice, but this aspect was beyond the scope of the present study.

Conclusion

PV reconnection and scar gaps on CMR are extremely prevalent in unselected patients 3 months after successful PVI. While both the scar burden and the extent of scar gaps on CMR correlate closely to the extent of PV reconnection, the performance of CMR to locate sites of PV reconnection remains limited, predominantly because of missed PV reconnections. CMR particularly lacks sensitivity to detect functionally relevant gaps on sites showing pre-existing fibrosis. Last, besides dramatic reduction in procedure duration, the use of circular multi-electrode catheters is associated with higher scar burden, fewer and smaller scar gaps, fewer reconnected veins after PVI, and a lower need for additional ablation to complete the lesion set during redo procedures.

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Disclosure

None.

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Table 1.	Population characteristics (N=51)	
Demogra	phics	
Age (years)		61±9
Female gender		12 (24%)
Cardiova	scular risk factors	
Hypertension		15 (29%)
Diabetes		0 (0%)
Dyslipidemia		14 (27%)
Smoking		13 (25%)
BMI		27±4
Obesity		14 (27%)
CHA2DS2-VASc score		1 [0-2]
Cardiova	scular history	
Mitral valve dysfunction on TTE		8 (16%)
CAD / ischemic cardiomyopathy		4 (8%)
DCM/HCM		1 (2%)
History of stroke/TIA/systemic emboly		5 (10%)
Duration of AF history (months)		36 [24-96]
Medicati	on	
Total number of AAD		1.9±1.0
Amiodarone		19 (37%)
Baseline	CMR	
LVEF (%)		63±7
LA volume (mL/m2)		57±11
LA fibrosis burden (%)		16.9±6.5
LA fibrosis UTAH stage (I/II/III/IV)		2/38/11/0
AF ablati	on procedure	
AF at the time of procedure		9 (18%)
Circular ablation catheter		23 (45%)
Success PVI before adensoine		51 (100%)
Additional ablation after adenosine		20 (39%)
Success PVI after adensoine		51 (100%)
Additional CFAE or linear ablation		7 (14%)
Additional ablation on CTI		14 (27%)
Total RF duration on PVs (min)		26±17
	RSPV (min)	7±6
	RIPV (min)	6±6
	LSPV (min)	7±6
	LIPV (min)	5±4
Total RF duration (min)		29±17
Fluoroscopy time (min)		35±23
Procedure duration (min)		164±69

AAD: anti-arrhythmic drug; AF: atrial fibrillation; BMI: body-mass index; CAD: coronary artery disease; CFAE: complex fractionated atrial electrograms; CMR: cardiac magnetic resonance; CTI: cavo-tricuspid isthmus; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LA: left atrium; LSPV/LIPV: left superior/inferior pulmonary vein; LVEF: left ventricular ejection fraction; PVI: pulmonary vein isolation; RF: radiofrequency; RSPV/RIPV: right superior/inferior pulmonary vein; TIA: transient ischemic attack
Table 2: Findings on follow-up CMR (N=	51)		
Cine imaging			
LVEF (%)	62±9		
LA volume (mL/m2)	54±11		
Scar quantification			
Total scar burden on LA (mL)	8.1±2.7		
Scar burden on PVs (mL)	7.8±2.1		
Scar on RPVs (mL)	4.1±1.0		
Scar on LPVs (mL)	3.7±1.3		
LA scar outside PVs	4 (8%)		
Scar on CTI	9 (18%)		
Scar gaps on PVs			
Prevalence of gaps per patient	39/51 (76%)		
Prevalence of gaps per vein*	78/200 (39%)		
Prevalence of gaps RSPV	22/51 (43%)		
Prevalence of gaps RIPV	27/51 (53%)		
Prevalence of gaps LSPV	16/51 (31%)		
Prevalence of gaps LIPV	13/47 (28%)		
Extent of gaps per patient (n sectors)	2.2±2.1		

* Computed on a total of 200 veins due to long common trunk of left veins in 4 patients. CMR: cardiac magnetic resonance; CTI: cavo-tricuspid isthmus; LA: left atrium; LSPV/LIPV: left superior/inferior pulmonary vein; LVEF: left ventricular ejection fraction; RSPV/RIPV: right superior/inferior pulmonary vein

Tabl	e 3: findings at follow-up EP procedure (N=5	1)
AF at	t the time of follow-up procedure	3 (6%)
Asse	ssment of PV reconnection	
F	Prevalence of reconnection per patient	45 (88%)
F	Prevalence of reconnection per vein*	99/200 (50%)
	Prevalence of reconnection on RSPV	29/51 (57%)
	Prevalence of reconnection on RIPV	26/51 (51%)
	Prevalence of reconnection on LSPV	23/51 (45%)
	Prevalence of reconnection on LIPV	21/47 (45%)
E	Extent of reconnection per patient (n sectors)	3.3±2.4
Addi	tional ablation	50 (98%)
1	Ablation on PVs	49 (96%)
4	Additional CFAE or linear ablation	12 (24%)
1	Additional ablation on CTI	11 (22%)
1	Total RF duration (min)	18±16
F	Fluoroscopy time (min)	43±31
F	Procedure duration (min)	166±74
Follo	ow-up at 1 year	
1	AF recurrence	10/51 (20%)
F	Paroxysmal AF	7/51 (14%)
F	Persistent AF	3/51 (6%)
AF: a	trial fibrillation: CFAE: complex fractionated atrial e	lectrograms: CTI:
cavo- super	tricuspid isthmus; EP: electrophysiology; I ior/inferior pulmonary vein; RF: radiofrequency; I rior/inferior pulmonary vein.	SPV/LIPV: left RSPV/RIPV: right

Table 4. EP and CMR characteristics according to the type of ablation catheter							
	Conventional	Circular					
Baseline characteristics	(N=28)	(N=23)	P value				
Age (years)	60±8	62±9	0.46				
Female gender	10 (36%)	2 (9%)	0.02				
CHA2DS2-VASc score	1 [0-2]	1 [0-2]	0.61				
Duration of AF history (months)	60 [24-108]	36 [24-81]	0.62				
Total number of AAD	1.9±1.1	1.9±0.8	0.96				
Amiodarone	9 (32%)	10 (43%)	0.42				
LVEF (%)	61±7	65±5	0.05				
LA volume (mL/m2)	56±11	57±11	0.89				
LA fibrosis burden (%)	17.1±6.5	16.8±6.4	0.82				
Index AF ablation procedure							
AF at the time of procedure	4 (14%)	5 (22%)	0.50				
Success PVI before adensoine	23 (100%)	28 (100%)	NS				
Additional ablation after adenosine	9 (32%)	11 (48%)	0.26				
Success PVI after adensoine	23 (100%)	28 (100%)	NS				
Additional CFAE or linear ablation	3 (11%)	4 (17%)	0.50				
Additional ablation on CTI	3 (11%)	8 (35%)	0.04				
Total RF duration on PVs (min)	38±15	11±4	<0.001				
Total RF duration (min)	41±14	14±5	<0.001				
Fluoroscopy time (min)	42±28	25±11	0.009				
Procedure duration (min)	206±58	109±33	<0.001				
3-month CMR							
Total scar burden on LA (mL)	7.4±2.8	9.0±2.4	0.03				
Scar burden on PVs (mL)	7.1±2.2	8.6±1.7	0.01				
Prevalence of gaps per patient	24 (86%)	15 (65%)	0.09				
Prevalence of gaps per vein	50/110 (45%)	28/90 (31%)	0.04				
Extent of gaps per patient (n sectors)	2.9±2.3	1.4±1.3	0.01				
3-month EP study							
AF at the time of follow-up procedure	2 (7%)	1 (4%)	0.68				
Prevalence of reconnection per patient	24 (86%)	21 (91%)	0.55				
Prevalence of reconnection per vein	62/110 (56%)	37/90 (41%)	0.03				
Extent of reconnection per patient (n sectors)	3.6±2.8	2.8±1.9	0.23				
Additional ablation	27 (96%)	23 (100%)	0.89				
Total RF duration (min)	23±17	13±13	0.03				
Fluoroscopy time (min)	51±33	34±26	0.06				
Procedure duration (min)	191±83	135±48	0.007				



Figure 1. Quantification of scar burden on CMR. On late gadolinium-enhanced images acquired 3 months after PVI (A) the LA wall is manually traced (B). Scar is segmented using histogram thresholding by applying the full width at half maximum method (C), with potential manual adjustment by an expert depending on image quality. This results in the identification of scar pixels within the LA wall (D). Scar distribution is analyzed by overlaying the maximum transmural intensities on a left atrial endocardial geometry (E). A color coding is applied to visualize scar heterogeneity, ranging from 50% (scar threshold) to 70% of the maximum signal intensity. For the quantification of scar burden, expressed in mL, connectivity thresholding is applied after histogram analysis, in order to remove isolated pixels related to image noise.



Figure 2. Detection of a scar gap on CMR after successful PVI. The analysis of scar maps shows a large gap on the superior segment of the LSPV (yellow arrows in A). To confirm the presence of a scar gap, native late gadolinium-enhanced images are reviewed in 2 perpendicular planes aligned on the LSPV axis (B and C), as well as in a stack of images parallel to the ostium (D, image orientation corresponding to the white lines in B and C). An enhancement defect is clearly visible on the superior segment of the LSPV (yellow arrows in D). Of note, scar on the LIPV is circumferential.



Figure 3. Circumferential scarring around the right pulmonary veins on CMR after PVI. The analysis of scar maps shows dense scar around both the right pulmonary veins. No enhancement defect is seen on native late gadolinium-enhanced images reformatted in 2 perpendicular planes aligned on the RSPV axis (B and C), as well as in a stack of images parallel to the ostium (D, image orientation corresponding to the white lines in B and C).





Figure 4. CMR markers associated with the extent of pulmonary vein reconnection after PVI. A: relationship between scar burden on CMR

and the extent of PV reconnection. B: relationship between the number of scar gaps detected on CMR and the extent of PV reconnection.



Figure 5. Distribution of scar on CMR after PVI with conventional single-electrode and circular multi-electrode ablation catheters. Scar maps are shown in 5 patients who underwent PVI with circular multi-electrode catheters (left panel), and in 5 who underwent PVI with single-electrode catheters (right panel). The distribution of scar on the left atrium is displayed in both posterior (left images) and anterior views (right images).

Chapter 3

DISCUSSION AND FUTURE PRESCPECTYIVE

Discussion

Pulmonary vein isolation (PVI) is the established therapy for symptomatic atrial fibrillation (AF) after failure or intolerance of antiarrhythmic drugs (AADs). A meta-analysis, including both randomized and nonrandomized clinical trials, reported 57% of success rate after single procedure, increasing to 71% after repeated procedure [461]. However, success rate in persistent AF was only 47% [461]. Pulmonary vein (PV) electrical reconnection is considered the dominant mechanism of recurrence [462] that limits long-term success and remains a current issue despite advances in catheter design, ablation techniques and AF treatment strategies. Other mechanisms such as electrical and structural atrial modelling forming other substrates (fibrosis) as a result of aging, heart failure, inflammation, diabetes and obesity contribute to AF recurrence and maintenance[417, 421, 422]. With 3D mapping system and image integration into these systems, point-by-point radiofrequency ablation is still relatively time consuming and complex. Balloon (cryoablation) and multielectrode circular ablation catheters (PVAC and nMARQ) were developed to overcome conventional procedure challenges. Nevertheless, cryoablation balloon is limited by its inability to adapt to anatomic pulmonary vein (PV) variability and to non-PV sites ablation, whereas PVAC catheter lacks irrigation and therefore increases the risk of thromboembolic complications. Inversely, nMARQ is an irrigated circular catheter which in addition to its role in PVI, allows for non-PV and left atrium (LA) substrate ablation in paroxysmal (PAF) and persistent AF (PsAF).

The main aims of the studies:

- Randomized comparison between circular, multielectrode catheter (nMARQ) versus conventional point-by-point single catheter (Navistar Thermocool) for PVI in PAF efficacy and safety, in addition to acute (index) and late (after 3 months of repeated procedure) electrical evaluation of reconnection rate and long term clinical outcome (1 year).
- 2. The role of circular catheter (nMARQ) in PsAF, especially non-PV sites ablation and linear lesions guided by 3D Carto (complex fractionated electrograms (CFAE) based ablation) with or without non-invasive mapping ECVUETM Cardioinsight (driver based ablation), and long term clinical outcome evaluation (1 year).
- 3. Lesions evaluation by delayed enhancement magnetic resonance (DEMRI) after PVI to predict, characterize and localize PV reconnection for future ablation guidance.

The major findings of the thesis:

- Circular catheter (nMARQ) was 3 times faster in isolating the pulmonary veins while preserving efficacy and safety.
- Circular catheter demonstrated shorter radiofrequency (RF) time for all veins, shorter procedural duration and less x-ray exposure, when compared to conventional catheter.

- Circular catheter was effective and faster for non-PV sites ablation and linear ablation (when required) in PAF and PsAF, therefore obviating the need for an additional ablation catheter in the majority of patients.
- Pulmonary vein reconnection after circular catheter ablation was fewer at 3 months in PAF, therefore, shortening the repeated procedure time.
- Circular catheter was effective in isolating the right inferior pulmonary vein (RIPV), the challenging vein to isolate with other technologies, showing lesser reconnection, both acutely (index procedure) and at 3 months (repeated procedure).
- Circular catheter demonstrates encouraging results for rapid, safe and effective ablation when guided by non-invasive mapping.
- The circular ablation catheter appeared to be safe with no major procedural complications in PAF and PsAF.
- Fatal atrio-oesophageal fistula occurred in other studies were associated with general anesthesia where clinical evaluation for pain while ablating was limited.
- PV reconnection and scar gaps was prevalent on repeated procedure and CMR after PVI at 3 months despite recurrence.
- CMR performance to predict PV reconnection sites seemed insufficient to provide relevant guidance for repeated procedure.
- Extent of PV reconnection was related positively to the number of gaps detected on CMR, and negatively to the scar burden on PVs.
- Circular catheter was associated with higher scar burden, fewer and smaller scar gaps, fewer reconnected veins after PVI, and lower need for additional ablation during repeated procedure.

Table 1: summarize studies conducted on nMARQ catheter.

Investigators	Shin[431]	Deneke[426]	Zellerhoff[423]	Rillig[432]	Scaglione[425]	Mahida[286]	Vurma[287]	Rosso[427]	Al Jefairi
Year	Mar. 2014	Apr. 2014	Jun. 2014	Oct. 2014	Dec. 2014	Jul. 2015	May 2016	Jul. 2016	2017
Aim	Feasibility, safety, and acute efficacy	Efficacy and acute safety (oesophagus and cerebral evaluation)	Feasibility and efficacy	Modified energy setting to minimize oesophageal injury	Feasibility, acute and short-term efficacy, safety (silent cerebral ischemia)	Multicenter Efficacy and safety	Safety and efficacy	Non- randomized comparison circular (nMARQ) versus point by point (smart touch, contact force)	Randomized comparison circular (nMARQ) versus point by point (Navistar ThermoCool)
Number of Patients	25	43	39	21 Group 1 = 6 Group2 = 15	25	374	327	86 (ST 50 patients, nMARQ 36 patients)	81 (TC 43 patients, nMARQ 38 patients)
AF type	PAF	PAF	PAF	PAF	PAF	PAF (263 patients) PsAF (111 patients)	PAF (228 patients) PsAF (97 patients)	PAF 57 patients PsAF 29 patients	PAF

Outcome parameters	Acute success rate in PVI	PVI, thermal oesophageal lesions and cerebral (SCL) evaluation	Acute success rate in PVI	Thermal esophageal injury (EI) incidence	Acute success rate in PVI (Lasso and nMARQ concordance)	Acute success rate in PVI Non-PV ablation 1 year procedural outcomes	Safety Acute success rate	Acute and long-term success rate	Acute success rate, reconnection rate, long term success rate
Follow up duration	4 ± 2 months	Post ablation Median 2 days	140 ± 75 days	Not evaluated	6 months	1 year	6 ± 5 months	PAF 18.4 months PsAF 19 months	3, 6 and 12 months
Freedom from AF at follow up	81%	93%	66%	Not evaluated	68%	PAF 65% PsAF 65%	PAF 75% PsAF 52%	PAF ST 85 vs nMARQ 82% (p = 0.785) PsAF ST 75 vs nMARQ 69% (p = 0.729)	TC 79% vs nMARQ 77% (p = 0.852)
PVI with nMARQ	100%	98%	98%	99%	96%	100%	Not evaluated	97%	100%
RF duration for PVI (min)	27 ± 11	19 ± 7	10.0 ± 4.6	Not available	14.9 ± 3.7	13.5 ± 6.4	PAF 18.9 ± 6.4 PsAF 22.1 ± 6.1	Not available	TC 38 ± 13 vs nMARQ 12 ± 5 (p < 0.001)
RF duration for non-PV (min)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	PAF 17.4 ± 13 PsAF 31.3 ± 24.8	Not evaluated	Not available	TC 15 ± 11 nMARQ 5 ± 3 (p = 0.014)

nMARQ RF parameters	25 W unipolar 15 W bipolar 60 seconds 36°	25 W unipolar, 15 W bipolar, 20 W (posterior) 60 seconds 45°	25 W unipolar 60 seconds 45°	G1: 20 W unipolar, 10 W bipolar (posterior) 60 seconds G2: 15 W unipolar, 10 W bipolar	20 W, 18 W (posterior), 25 W (ridge) 40 seconds 45°	25 W unipolar 20-25 (posterior) 15 W bipolar 60 seconds 45°	18 W (men) 16 W (woman) 60 seconds 45°	25 W (anterior) 15 W (posterior) 60 seconds	25 W 20 W unipolar (posterior) 60 seconds 45°
Total procedure time (min)	94 ± 16	90 ± 210	86 ± 29	223 ± 53	131 ± 49	114 ± 42	PAF 68.6 ± 22.5 PsAF 75.0 ± 22.7	PAF ST 99.3±14.6 vs nMARQ 88.2±14 (p = 0.005) PsAF ST115±17 vs nMARQ 125±24 (p = 0.200)	TC 202 ± 52 vs nMARQ 111 ± 35 (p < 0.001)

Fluoroscopy duration (min)	9 ± 2	8–37 (range)	22.2 ± 6.5	35.5 (median)	1.8 ± 2	24 ± 14	PAF 14.8 ± 6.6 PsAF 16.8 ± 6.3	PAF ST 24.8 ± 6.3 vs nMARQ 23.1 ± 8 (p = 0.374) PSAF ST 23.8 ± 4.9 vs nMARQ 30.2 ± 10.5 (p = 0.038)	TC 46 ± 27 vs nMARQ 26 ± 11 (P < 0.001)
Acute PV reconnection rate	36%	35% (nMARQ)	26% (adenosine)	Not evaluated	22% (lasso)	Not evaluated	Not evaluated	Not evaluated	TC 53 vs nMARQ 41% (P = 0,270)
Acute reconnected vein	Not evaluated	LSPV LIPV	RSPV	Not evaluated	LSPV Ridge	Not evaluated	Not evaluated	Not evaluated	TC LSPV (anterior segment) vs nMARQ RSPV (anterior segment)
Freedom from AF recurrence after repeated procedure	Not evaluated	Not evaluated	77%	Not evaluated	Not evaluated	17 patients only/374 had recurrence	PAF 90% PsAF 83%	Not evaluated	TC and nMARQ 84% (p = 0.978)

Reconnection rate at repeated procedure	Nit evaluated	Not evaluated	90%	Not evaluated	Not evaluated	94%	Not evaluated	Not evaluated	TC 83% vs 87% (0.728)
Reconnected vein in repeated procedure	Not evaluated	Not evaluated	LSPV (antero- superior, carina) LIPV (anterior) RSPV and RIPV (antero- superior)	Not evaluated	Not evaluated	RSPV(anterior) RIPV (inferior) LSPV (superior)	Not evaluated	Not evaluated	TC LSPV (anterior) nMARQ RIPV (inferior))
Minor complications	0	0 SCL (33%) Thermal esophageal lesion (33%)	Cardiac tamponade	Charring 14% without embolism	Groin hematoma	0	Groin hematoma, transient ST elevation, pericardial effusion	0	Arteriovenous fistula and femoral artery aneurysm (repeated procedure)
Major complications	0	0	0	Phrenic nerve palsy, Severe EI in G1 50% and G2 7%	0	Fatal oesophago- pericardial fistula Mortality from sepsis of unknown origin ? PAS or PsAF	Fatal atrio- oesopageal fistula (1 PAF, 1 PsAF)	0	Renal infarction due to AF in nMARQ, LIPV stenosis and LSPV thrombosis in TC (after repeated procedure)

Efficacy in PVI and non-PVI ablation, reconnection rate and success rate in paroxysmal atrial fibrillation

Feasibility and efficacy (table 1): Our results are in line with previous studies demonstrating the feasibility and efficacy of nMARQ in PVI, reaching a range between 96 to 100%[286, 423, 425-427, 431, 432]. Acute PVI using cryoablation was 78% as reported in a systematic review of a total of 23 studies, including 1221 patients[429]; and 98% using PVAC[463].

Procedural parameters: atrial fibrillation ablation with nMARQ (figure 1) is associated with short procedure and fluoroscopy time (86 ± 29 minutes, 22.2 ± 6.5 minutes, respectively) compared with other ablation catheter designs[423]. The procedure time in cryoablation was 124 ± 39 minutes, and the fluoroscopy time was 21.7 ± 13.9 minutes, while in PVAC, procedure time mean was 129 minutes and the fluoroscopy time was 24 minutes[458, 463]. In our study, procedural parameters including radiofrequency (RF) time (nMARQ 14 ± 6 versus TC 43 ± 14 minutes, p < 0.001), procedural time (nMARQ 111 ± 35 versus TC 202 ± 52 minutes, p < 0.001) and fluoroscopy time (nMARQ 26 ± 11 versus 46 ± 27 minutes, p < 0.001) were significantly lower when compared to point-by-point (Navistar ThermoCool). In a non-randomized comparison of circular (nMARQ) versus point-by-point (Smart Touch (ST)), procedural time only was shorter with nMARQ (nMARQ 88.2 ± 14 minutes versus ST 99.3 ± 14.6 minutes, p = 0.005); fluoroscopy time was similar in both groups (nMARQ 23.1 ± 8 minutes versus ST 24.8 ± 6.3 minutes, p = 0.374) and RF data was not available to compare and elucidate the ablation efficacy between used catheters[427]. A prospective observational study of 175 patients who underwent PVI for symptomatic AF with 5 months follow-up using PVAC versus nMARQ

demonstrated that both technologies have short procedure and fluoroscopy time with comparable complication rates and comparable acute and 1 year success rate[464]. However, total procedure and RF time were shorter with nMARQ[464]. More RF application were needed in PVAC due to the inability to see PV signals during RF delivery, therefore, it is difficult to evaluate PV disconnection[464]. The efficacy of nMARQ over other catheters were due to the advantage of nMARQ technology in visualization of catheter location in PV ostia, the ability to create LA voltage 3D mapping, adding location point using Carto-merge technology and the adapting energy used (uni or bipolar). The nMARQ catheter has larger diameter (compared to PVAC) and therefore was almost always out of the vein[464].

Non-PV sites ablation: nMARQ had the advantage on cryoablation for non-PV site ablation, CTI ablation using nMARQ was tested initially in 4/10 patients in whom 2 patients shifted to conventional ablation to obtain bidirectional block[423]. Additional ablation (when necessary) with nMARQ at non-PV sites in PAF was performed in 36/263 patients (14%) in a multicenter study with 17.4 \pm 13 minutes of RF duration in whom 7 patients shifted to conventional ablation[286]. We demonstrated an effective and a faster non-PV nMARQ ablation in 37/38 patients (97%) when compared to Navistar ThermoCool (RF for non-PV sites, nMARQ 5 \pm 3 versus TC 15 \pm 11, p = 0.014) without a cross over.

Acute PV reconnection after index procedure: following RF catheter ablation, PV electrical reconduction due to incomplete lesions involve 24 to 50% of veins and re-isolation improve success rate[465-472]. Achieving durable PVI necessitates the creation of transmural, contiguous

ablation lesions encircling the vein circumference therefore, nMARQ catheter was developed to obtain continuous, circumferential and transmural lesions to reduce the recurrence rate because of the fixed distance between each ablation electrodes versus much less controlled RF delivery when performed by point-by-point (conventional) approach. Acute PV reconnection rate and the most frequent PV reconnection associated with nMARQ catheter were described in three previous studies: 35% (LSPV and LIPV), 26% (RSPV) and 22% (LSPV, ridge) respectively[423, 425, 426]. Compared to our study, acute reconnection rate was 41% (RSPV, anterior segment) in nMARQ and 53% (LSPV, anterior segment) in Navistar Thermocool (p = 0.270). This might point towards the restoration of transient conduction block caused by gaps from non-transmural or incomplete lesions in the ablation line that caused by local tissue inflammation and edema in viable myocardium sites, despite the waiting period of 30 minutes and adenosine injection that was used to unmask dormant conduction and minimize PV reconnection[234, 473-475]. Catheter instability or poor catheter-tissue contact in certain challenging PV anatomical segments such as the ridge or larger vein diameter could explain the frequent PV reconnection sites. It is well known that lesion size during RF ablation correlates with contact force, that may be low in nMARQ catheter due to helix-like design, causing small lesions[432, 476] Moreover, type of anaesthesia may play another role in catheter stability and PV reconnection [477, 478]. In addition to the mechanical concern in nMARQ design reducing the catheter contact, the nMARQ electrodes had technical issue in delivering enough energy to create transmurality. Other factors that could explain reconnections is physician experience and skill that may play a role in success rate. Therefore, efforts to enhance catheter stability such as enhancing anatomical details and developing better catheter designs and technologies might improve AF ablation

outcome[479]. In addition, we observed that the circular catheter was effective in isolating the RIPV, the technically challenging vein to isolate with other technologies and nMARQ (difficult to position) [431, 432], and showed significant lower reconnection rate in nMARQ group (nMARQ 3% versus TC 16%, p = 0.044). Our study showed heterogeneous efficacy of the nMARQ catheter, with superiority on the RIPV, particularly on the posterior segment, and at the ridge between LAA and LSPV. This may reflect better catheter stability and contact as RF lesion depth and dimensions are strongly influenced by catheter-tissue contact, catheter orientation and stability [479, 480]. This observation may guide improvements in performance on other veins and segments. The non-randomized study previously described has not evaluated the acute reconnection rate to compare results, but long term success (18 months) for PAF (freedom of AF, atrial flutter or atrial tachycardia) was 72% [427]. A study on the impact of RF characteristics on acute PV reconnection after adenosine injection to unmask PV reconnection and clinical outcome after PVAC-guided PVI ablation was conducted in 40 patients, showing that acute PV reconnection was observed in 24% and additional ablation of reconnection improves 1-year clinical outcome (freedom of AF) to 85% after single PVAC procedure [481]. When nMARQ compared to PVAC, acute success rate was comparable (78/82 patients (95%) versus 90/93 patients (97%), p = 0.6), respectively [464]. Acute PV reconnection after cryoablation was evaluated using the Achieve catheter over 30 minutes observation (spontaneous) and after adenosine challenge and found in 6/50 patients (12%), and was a low 4% of initially isolated PV and patients with right sided branching frequently experiencing reconnections [482]. Lower nadir temperature and longer rewarming time are associated with absence of acute PV reconnection and successful isolation in cryoablation [482]. After a mean follow up of 7.0 ± 1.7 months, 86% of patients were free from AF

and none of those with PV reconnection experienced recurrences[482]. Overall, acute PV reconnection was common despite the catheter technology used, waiting period and adenosine challenge. Further waiting period exceeding 30 minutes might be technically challenging waiting for transient conduction block to resolve. A repeated procedure still is a better option to increase long-term outcome and success rate. Common reconnecting PV segment as by know are well known, could be evaluated by pre-procedural imaging technique to evaluate PV anatomy and diameter. Therefore, catheter technology choice 'once it is possible and accessible' could be adapted to the patient accordingly. In addition, re-ablating common reconnecting PV sites 'security ablation' could be an option to reduce reconnection rate.

Late PV reconnection in repeated procedure: PV reconnection was ranging from 61 to 97% of previously isolated PV in patients undergoing repeated PVI after recurrence that reflect poor catheter contact [467, 468, 483]. In our study, late PV reconnection rate (at 3 months) has been evaluated by an offered systematic repeated procedure despite symptoms or recurrence, demonstrated fewer PV reconnection rate with nMARQ. Again, RIPV has less reconnection rate with nMARQ showing the efficacy of this catheter in treating this vein particularly. Precisely, nMARQ catheter was effective in ablating the posterior segment of RIPV (nMARQ 13 % versus TC 34%. p = 0.053) and the anterior segment of LSPV (nMARQ 10% versus 41 %; p = 0.006). In the multicenter study on nMARQ catheter, repeated procedure was performed in 15/263 patients only, illustrated the most frequent points of reconnection in RSPV (anterior segment), RIPV (inferior segment) and LSPV (superior segment). In our study, we confirm the most frequent points of reconnection in nMARQ were RIPV (inferior segment) and LSPV

(superior segment) in contrast to the RSPV (anterior segment) as prescribed in the multicenter study. Of note that the later study, data on the specific reconnection point were available in 15/263 patients and RSPV reconnection was secondary to catheter instability. In a prospective study investigated PV reconnections in repeated procedure and its special distribution after single irrigated tip antral ablation and duty cycled ablation (PVAC) used for PVI for the index procedure showed that the number of PV reconnection was similar in both groups (single tip 2.9 \pm 0.9 versus PVAC 3.2 \pm 0.7, p = 0.193) and the inferior segment of RIPV was significantly more vulnerable to reconnection after previous PVAC ablation, whereas the superior segment of RSPV showed significantly more reconnection in the RF group [484]. A multicenter analysis comparison of 2002 patients between cryoballoon 186/1126 patients (16.5%) and point-by-point open irrigated, non-force sensing RF 174/876 patients (19.9%)) evaluated late PV reconnection by repeated procedure at 11 ± 5 months [485]. The study showed that during followup, the incidence of atrial flutter/tachycardias was lower (19.9 versus 32.8 %, p = 0.005), fewer patients exhibited PV reconnection (47.3 versus 60.9 %; p = 0.007) and fewer PVs had reconnection (18.8 versus 34.6 %; p = 0.001) with cryoablation versus RF, respectively [485]. With cryoablation, the RIPV and the left common PVs were more likely to exhibit late reconnection due to the challenging anatomical vein orientation and larger diameter, respectively, decreasing the efficacy of balloon contact and occlusion, whereas LSPV was more likely to exhibit late reconnection with RF due to the difficulty in catheter stability in the ridge area[485].

 Table 2: summarize studies conducted on nMARQ catheter in persistent atrial fibrillation.

PsAF	Mahida[286]	Vurma[287]	Rosso[427]	Al Jefairi
Year	2015	2016	2016	2017
Study	Multicenter Efficacy and safety	Safety and efficacy	Non-randomized Circular (nMARQ) versus point-by-point (smart touch, contact force)	Efficacy and safety Non-PV ablation Non-invasive mapping 1 year outcome
End point	Safety and efficacy	Safety and efficacy (single procedure success rate)	PVI acute and long-term success	Safety and efficacy combined with noninvasive mapping Long term clinical outcome
Procedural end point	Cardioversion following PVI or non-PV sites ablation + lines for AF termination to SR	Lines for AT	non-PV sites ablation (CFAE) + lines for AF termination to SR	non-PV sites ablation (CFAE or drivers) + lines for AF termination to SR
Number of Patients	111 patients	97 patients	Smart Touch (ST) 16 patients nMARQ 13 patients	50 patients
Follow up	1 year	6 ± 5 months	19 months	3, 6 and 12 months
PVI	100%	Not evaluated	100%	100%
Non-PV	30 patients (27%)	Not available	ST 5 patients nMARQ 5 patients	46 patients (92%)

Non-PV radiofrequency (min)	31.3 ± 24.8	Not available	Not available	17.24 ± 12.42
RF time (min)	Not available	22.1 ± 6.1	Not available	31.13 ± 17.31
Success rate at follow up	65%	52%	ST 12/16 (75%) nMARQ 9/13 (69%) P = 0.729	66%
Procedural time	PVI only 1.9 ± 0.7 hours + non-PV 2.4 ± 1 hours	75.0 ± 22.7	ST 115±17 minutes nMARQ 125±24 p = 0.200	3.18 ± 1.03 hours
Fluoroscopy	24 ± 14 minutes	16.8 ± 6.3	ST 23±4.9 nMARQ 30;2±10.5 p = 0.038	45.53 ± 22.46
Complications	Fatal oesophagopericardial fistula Sepsis of unknown origin	Fatal atrio-oesophageal fistulas	0	Steam pop Transient ischemic stroke
Repeated procedure success rate	2 patients only	83% in 5% redo cases	Not applied	Not applied

Efficacy and success rate in persistent atrial fibrillation (table 2)

NMARQ success rate and short procedure time in PsAF was reported in previous studies and was comparable to our study, ranging between 52 to 69% and 75.0 ± 22.7 minutes, respectively[286, 287, 427]. We demonstrated that nMARQ catheter is highly effective in achieving successful PVI (100%) and feasible for non-PV targets including: complex fractionated atrial electrogram (CFAE) or driver based ablation,

linear ablation (roof (50%) and mitral line (80%)) cavotricuspid isthmus line (80%). Previous studies on nMARQ catheter evaluated PVI as previously discussed. Three of these studies evaluated nMARQ in PsAF[286, 287, 427] and was reported to be effective in non-PV ablation in one study that showed 30/111 patients (27%) underwent non-PV ablation where nMARQ ablation alone on non-PV sites was effective in blocking CTI and roof lines with a limited number of RF application (6.0 ± 4.9 minutes, 4.8 ± 2.9 minutes, respectively) without the need for additional ablation with conventional catheter [286]. The nMARQ catheter was also effective for simultaneously targeting multiple left and right atrial sites with high-frequency fractionated signals [286]. In our study in contrast, 19/50 patients (38%) had linear ablation with nMARQ catheter for atrial tachycardia (AT). Linear block was obtained in 13 patients (68%), in whom 9 patients (70%) had block with nMARQ only catheter with RF duration of 16 ± 14 minutes. The procedure time for PsAF with PVI only was 75 minutes [287] and PVI with additional non-PV sites ablation was 144 minutes [286]. Cavotricuspid line for flutter was performed in 27 patients (54%) and CTI block was obtained in 24 patients, in whom 19 patients (79%) had CTI block with nMARQ catheter only with RF duration of 3 ± 2 minutes. A conventional catheter was required for line block to obtained by nMARQ catheter. We reported 180 minutes including non-invasive phase mapping time. In the nonrandomized study comparing nMARQ to smart touch, procedural time was similar regardless of the catheter used (smart touch 115 ± 17 minutes versus nMARQ 125 ± 24 minutes (p = 0.200)). AF was terminated (sinus rhythm (SR) or atrial tachycardia (AT)) in 37/50 (74%) guided by invasive Carto 3 mapping with CFAE ablation and in 25/32 (78%) guided by non-invasive mapping. Longer procedure time in our study was due to the additional time included in non-invasive mapping in addition to the electro-anatomical invasive mapping and ablation required

for non-PV or linear. In the non-randomized study, difference in procedure protocol such as procedure conduction under general anaesthesia, angiography to visualize PV, single operator experience renders technical facilities and efficacies into procedure[427], whereas due to different procedural endpoint (lines only without CFAE ablation) was performed in the study concluding the shortest procedure duration[287].



Figure 1: Isolation of left inferior pulmonary vein (LIPV) during nMARQ. (A) fluoroscopic image of NMARQ catheter at the LIPV ostium. (B) three-dimensional left atrial anatomy demonstrating nMARQ ablation catheter at the LIPV ostium and RF lesions at the ostia of all 4 pulmonary veins (PV) (red circles). (C) intracardiac electrograms recorded from nMARQ catheter in LIPV demonstrating PV isolation (PVI) during radiofrequency (RF) delivery. PV signals are indicated in red squares[286].

Safety in paroxysmal and persistent atrial fibrillation ablation

Several studies have reported on complications following AF ablation with nMARQ catheter accounting a total number of 940 patients in 8 studies[286, 287, 423, 425-427, 431, 432]. Major complication occurred in 5 patients (0.5%) including 4 deaths (0.4) [286, 287, 432]: 1 phrenic nerve palsy during right PV ablation[432], 1 fatal oesophago–pericardial fistula[286], 1 death due to sepsis from unknown source after nMARQ ablation[286], 2 fatal atrio–esophageal fistulas (figure 2)[287]. The mortality rate with nMARQ catheter seems higher than the 0.1% reported with conventional catheters[293], however, it is important to highlight that the later involved a larger population (> 30,000 patients) and was a registry based on physician willingness to declare complications.

Oesophageal injury (EI): oesophageal lesions after PVI was described after conventional RF ablation and multipolar non-irrigated PVAC catheter; the incidence of oesophageal wall injury was reported to be up to 18% and 8%, respectively[290, 486]. The irrigation system in nMARQ catheter optimizes energy delivery to the tissue and therefore may change the risk profile for oesophageal injury compared with PVAC catheter. However unexpectedly, high incidence of thermal oesophageal injury was reported following PVI using nMARQ of 33% in 43 patients with an energy power used of 20–25 W at posterior wall using unipolar ablation, maximum temperature of 45°C and RF duration of 60 seconds; and up to 50% in 6 patients with an energy power of 15–20 W at posterior wall using unipolar ablation, maximum duration of 60

seconds or 10 W using bipolar ablation with maximum duration of 30 seconds [426, 432]. In the later study, the optimal power setting was recommended, therefore, to reduce the incidence of esophageal injury and a comparable incidence with conventional PVI procedure was reported when power settings of 10 W of bipolar ablation in the posterior LA wall and RF application time of 30 seconds were reduced to 6.7% at the posterior LA[432]. Of note, the later study suggests that clinically relevant reduction rate of oesophageal injury from 50% to 6.7 is overwhelming due to the limited cohort size[432]. In our and other studies on nMARQ safety, no major complications of Oesophageal injury or mortalities were observed except for one acute cardiac tamponade in our study [423, 425, 427, 431]. However, pulmonary vein stenosis (in Navistar ThermoCool group) and renal embolism due to AF recurrence (in nMARQ group) occurred after repeated procedures with the conventional catheter. Though, we didn't use Oesophageal temperature monitoring or systematically perform post ablation endoscopic evaluation to document thermal esophageal damages specifically. Hence, studies in larger cohorts of patients are necessary to define the mortality rate associated with nMARQ ablation. More specifically, mild thermal oesophageal damage (superficial ulcerous lesion) occurred in 2/43 patients (5%) only with increased oesophageal temperature [426]. The incidence appeared higher compared to patients treated with other ablation technologies [289, 487]. In patients treated with irrigated RF single-tip, oesophageal ulcers were identified in up to 11% and thermal oesophageal damage in 30-46% of patients using endoluminal oesophageal temperature monitoring. The implication following the safety profile suggests energy settings adaptation especially at the posterior LA. Oesophageal temperature monitoring may be advised for monitoring to reduce oesophageal damage, because the oesophagus is broad, the lateral position of the temperature probe

or mapping electrode might not align with the ablation electrode, and the operator could receive a false impression, of safety[155, 488]. We did not monitor oesophageal temperature routinely during ablation because the procedure was under local anaesthesia instead of general anaesthesia, which facilitates the use of probe during the procedure. Performing local anaesthesia was preferred strategy in our institution to keep the patient in contact for any clinical evaluation throughout the procedure. Interestingly, fatal oesophageal-pericardial fistula occurred in previous studies was with general anaesthesia, therefore the clinical evaluation such as pain was limited. We perform ablations procedure under local anaesthesia and sedation, in addition to the caution we add in posterior LA ablation by adapting the energy settings, such complication did not occur in our series and other series using the same method[423, 425-427].



Figure 2: Right: intraoperative view from left atrium of atrio-oesophageal fistula of the first patient with persistent atrial fibrillation (PsAF). Left: endoscopic view of atrio-oesophageal fistula after cardiac surgery[287].

Silent cerebral lesions (SCL): serious safety concerns regarding silent cerebral lesions (SCL) caused by multielectrode ablation in the LA were arisen[433, 434]. No major procedural complications and no SCI in 25 patients evaluated by 24-hour post procedural cerebral diffusion weighted DW-MRI were reported [425]. In contrast, a study on 43 patients showed that 14 patients (33%) had SCL following PVI ablation with nMARQ, was slightly higher compared to single-tip irrigated RF (24%) or cryoballoon (21%) when using comparable MRI follow-up technology and definition and consistent (37%) with rates reported using PVAC [426, 433, 489]. Incidence of ablation related asymptomatic cerebral events (ACE) was between 2% and 41% [433, 448-452, 454, 456, 490, 491]. The PVAC was associated with highest rates of ablation-related ACE due to non-irrigated radiofrequency ablation, which increased the risk of thrombus formation. Neurological embolic complications with multielectrode ablation catheter such as the PVAC catheter was 0.63% in a meta-analysis [458]. The nMARQ system has some similarities to the PVAC ablation catheter but the difference is that the nMARQ catheter is continuously irrigated [334, 405, 492]. None of the previous studies on nMARQ reported clinical stroke [286, 287, 423, 425-427, 431, 432]. Comparison between PVAC and nMARQ showed that the related silent cerebral events (SCE) rate is similar between both groups [433, 448-450, 452, 454, 456, 490, 491]. In contrast, a randomized study comparing the incidence of SCE after PVAC, nMARQ and thoraco-scopic surgical AF ablation reported higher number of ablation-related SCE in the PVAC: 2 patients (13.3%), 1 patient (6.7%) in nMARQ with one patient that did not resolve at 3 months and no surgical patients with ablation-related ACE [459]. The study reported high background prevalence of MRI-detected cerebrovascular disease at baseline that was not ablation related (5.1%) and at 3 months (3.3%). In a systematic review of PVAC ablation, the overall procedural complication rate appeared
to be low (acute procedural complications were 2%, though non-uniform screening may limit the accuracy of this estimate)[458]. However, high rates of silent cerebral ischemic lesions (38%-45%) have been reported, significantly higher than with irrigated RF (7%-17%) or cryoablation (4%-6%)[458]. We did not acquire cerebral imaging post ablation to evaluate post cerebral lesions in our cohort since the study was focused on studying reconnections, though cerebral imaging evaluation could be interesting to study in this population. The circular catheter is a single ablation approach for simultaneous mapping and ablation avoiding the need for other use for mapping catheters after PVI, therefore, embolisms risk was lower during catheter manipulation throughout the long sheath. However, a transient ischemic stroke occurred after ablation in our series and resolved without sequela.

Phrenic nerve palsy (PNP): Phrenic nerve injury (PNI) are more commonly reported with cryoablation up to 11%[358]. It is self-resolving in the majority of cases but resolution is sometimes long[493]. The complication rate in cryoablation reported in a systematic review was relatively low with 6% incidence of phrenic nerve palsy (PNP), most of them being transient[429]. Two cases of PNP after AF ablation with nMARQ was reported using 15 W in RPV resolved partially after 6 months (figure 3) [423]and fully after 5 days, respectively[432, 494]. We didn't observe any phrenic nerve injury in PAF and PsAF ablation with nMARQ.



Figure 3: (A) Fluoroscopy. (B) cartography of the procedure. (C) Chest x ray revealing phrenic nerve palsy (PNP)[494]

Long term outcome in paroxysmal atrial fibrillation

Singles procedure 1 year success rate using nMARQ was ranging between 65% to 83%[286, 287], similar to conventional RF catheters (67%)[460]. Long term (\approx 18 months) was 80% in the non-randomized comparison of nMARQ versus contact force study [427]. In our study, 77% versus 70% of patients were in sinus rhythm at 1 year in nMARQ and Navistar Thermocool, respectively. Single procedure 30 months success rate was 40% versus 42% and repeated procedure success rate was 72% versus 76% in RF versus cryoballoon, respectively[495].

Success rates after one and repeated procedure were 66% and 77%, respectively, similar to the success rates reported in conventional RF and multielectrode ablation and higher than in cryoablation[352, 437]. Rates from AF recurrence after 6 months of single PVAC ablation procedure, including repeated procedures, were 68%[463]. In PVAC versus nMARQ study, one year freedom from AF was 79% versus 81, respectively[464].

Long term outcome in persistent atrial fibrillation

In the meta-analysis of 6 studies reporting outcomes of PsAF ablation with conventional catheter, 1-year success rate was 52%. [460] In the multi-center cohort study of nMARQ catheter for PsAF, 65% of patients were free from AF at 1 year[286], although these results should be interpreted with caution because of significant heterogeneity in the ablation strategy, the additional use of conventional ablation catheter to nMARQ and the small number of patients (20/111 patients (18%)) in the follow up data. Whereas the success rate was similar in the non-randomized comparison between contact force and nMARQ (ST 75 % versus nMARQ 69%)[427]. In the largest single-center series where PVI only was treated with PsAF ablation, 6 months success rate of 52% was reported[287]. The present study identified a success rate of 55% and 66% arrhythmia free at 6 months and 12 months in the available data of 22/50 (44%) and 38/50 (76%) patients, respectively. In contrast, procedural and one year PVAC follow up freedom from PsAF was 62[496]. Despite developed mapping and ablation technologies in PsAF,

catheter ablation for rhythm control remains challenging. There is no single strategy is consistently effective in this population. The catheter ablation success depends not only on the procedure technical aspect but also on patient heterogeneous related factors such as AF duration in association with comorbidities. As supported by clinical evidence and related to the significant atrial remodelling, substrate modification should be sought in every patient, in addition to the essential steps of PVI and non-PV triggers identification and ablation to achieve longterm success. Moreover, outcomes improve with aggressive medical treatment of risk factors reduction and after repeat procedures[497-499]. New techniques and targets currently under investigation could prove importance in treating PsAF and improve long term success, however longer randomized controlled trials are needed to evaluate the long term effectiveness and safety.

Atrial scar on cardiac magnetic resonance and pulmonary vein reconnection

A first large direct comparison of scar distribution on cardiac magnetic resonance (CMR) and PV electrical reconnection characteristics in 51 consecutive patients underwent PVI for PAF, regardless of AF recurrence. In addition, another comparison of scar burden and distribution on CMR between single electrode and multielectrode catheters was undertaken. Our results confirm that PV electrical reconnection and scar gaps on CMR are extremely prevalent after successful PVI at 3 months. While scar burden and scar gaps extent on CMR correlate closely to the extent of PV electrical reconnection, the ability of CMR to locate PV electrical reconnection sites remains limited because of missed PV reconnections. CMR sensitivity was limited on sites showing pre-existing fibrosis that add a challenging point to differentiate fibrosis

from scar tissue. Last but not least, in addition to the reduction in procedure time and RF duration, the circular multielectrode ablation catheter was associated with higher scar burden, fewer scar gaps, and fewer reconnected veins on CMR after PVI.

Scar burden quantification: CMR is a direct method for lesion characteristic assessment and visualization following ablation using delayed gadolinium enhancement (DE)[174-177]. Scar measurement in our study was expressed by mL, taking into account scar thickness to make scar measurements less dependent on atrial wall segmentation, while previous studies reported scar surface measurements or scare volume indexed on atrial wall volume [193, 500]. The rational was to take into account scar thickness and to make measurements less dependent on atrial was segmentation. Our results in term of scar burden after PVI were consistent with previous study using the same approach[501]. In our study, we confirm that the scar burden after PVI was variable between patients ranging from 2.8 to 16.7 m, despite the standardized ablation protocol. In addition, the study showed poor correlation between RF duration and scar burden. Therefore, the ability to transform acute ablation lesions into chronic scar was patient-dependent.

Scar gaps were identified on 3D scar maps and confirmed by visual inspection of native images with a second LGE dataset systematically acquired in the sagittal plan, closer to the orientation of PV ostia. We found scar gaps was prevalent on CMR after PVI and this was consistent with previous study[502].

PV reconnection was common and high even in patients with no recurrence[503, 504]. This is explained by recovered PV reconnection from reduced tissue conductivity and transient conduction block caused by resolved inflammation, edema and heating from ablation is actually still viable myocardium areas[474]. In the present study, despite the systematic use of adenosine to unmask dormant conduction to overcome this phenomenon[469], the reconnection rate was still high.

Scar gaps and PV reconnection relationship: previous studies reported on the correlations between post ablation scar on CMR and patient outcome after PVI[193, 505]. Conflicting results were reported with some studies demonstrating good correlation, suggesting the use of CMR scar maps to guide repeated procedures[506, 507], whereas other studies demonstrated poor correlation[508, 509]. In the present study, CMR and EP characteristic after PVI were systematically compared at 3 months and we found significant but poor correlation between scar gaps on CMR and PV reconnection. Particularly, CMR lacks sensitivity to predict sites of PV reconnection and interestingly, this sensitivity issue seemed to be partly due to the confounding effect of pre-exciting fibrosis. Indeed, very few segments with gaps showed fibrosis on baseline CMR, while a majority of false negative segments (PV reconnection with no gap on CMR) showed fibrosis. Thus, a major limitation of CMR appeared to be the inability to distinguish scar from pre-existing fibrosis. However, a significant number of PV reconnections missed by CMR occurred in segments showing no pre-existing fibrosis. These may be explained by the inability of CMR to characterize scar transmurality, because of insufficient spatial resolution as supported by a study relating PV reconnection and incomplete scar transmurality

on histopathology[510]. Other factors besides lesion discontinuity can interfere including the scar gaps geometry[511], fibres direction in the gap area[512], and potential source-sink effects. Overall, CMR is the current imaging modality to evaluate scar or gaps notably through LGE, and its performance to predict PV reconnection sites seemed insufficient to provide relevant guidance for repeated procedure.

Scar burden and PV reconnection relationship: we found that the extent of PV reconnection was related positively to the number of gaps detected on CMR, and negatively to the scar burden on PVs. This finding supports the use of post-ablation CMR to predict patient outcome[193, 505]. However, other studies showed that PV reconnection does not directly imply to AF recurrence because of other factors that might play some role[503, 504]: (1) the ring reconnected vein might not be the one hosting the triggers responsible for AF episodes. (2) even if triggers were present in the vein, these might have been directly eliminated by ablation despite incomplete PVI. (3) the conduction block, although incomplete; may be sufficient to render PV triggers less arrhythmogenic. Generally, PV reconnection was common, even in the absence of AF recurrence, and localizing reconnection site by MRI might not be the best strategy, while quantifying the degree of reconnection might be more appropriate and accessible aim.

Impact of circular multielectrode ablation catheter: circular multielectrode catheter technology was developed to create more complete circumferential lesions during PVI by delivering RF energy simultaneously from multiple electrodes. However, their ability to actually improve

lesion circumferentially remains unknown, and scar characteristics after PVI has not been thoroughly studied. Using an irrigated decapolar circular catheter (nMARQ), our study showed that the technology achieved successful PVI in shorter procedure time as compared to a conventional single electrode irrigated ablation catheter as prescribed earlier. More importantly, when analysing scar lesions using CMR at 3 months, we found that (1) circular catheter created higher amounts of scars on PV, (2) less veins with scar gaps, and (3) lower extent of gaps per patients. The repeated electrophysiology (EP) study confirmed that the thorough lesions were associated with less reconnected veins, therefore, the need for additional ablation during repeated procedure was reduced with shorter RF duration and procedure time (conventional catheter only was used in repeated procedure). We acknowledge that the immediate clinical implications of our finding might be limited, knowing that the catheter used in the present study was recalled from the market due to significant thermocouple issues and to fatal reports of oesophageal fistulas[286, 287, 513]. However, our results support future developments of the circular multielectrode catheter ablation technology, as it may both reduce PVI procedure time and improve efficacy.

Thesis limitations

The first study was a single center randomized comparison between circular multielectrode catheter (nMARQ) and point-by-point single electrode catheter study in PAF that didn't meet the planned enrolment target. The catheter withdrawal from the market in June 2015 interrupted patient recruitment into the study. However, the patient cohort recruitment was sufficient to demonstrate statistically significant results. The second study on the role of circular multielectrode catheter (nMARQ) in PsAF, a non-randomized single center study and the follow up date was available only in 76% of patients. We did not monitor oesophageal temperature routinely during ablation or perform post ablation oesophageal endoscopy or cerebral imaging because oesophageal monitoring requires general anaesthesia to help the patient handle the probe during the procedure, whereas cerebral imaging evaluation was beyond the study scope. However, we did not observe any oesophageal or cerebral complications related to the circular catheter, possibly as a consequence of reduced power and duration of RF delivery in the posterior wall, the single catheter approach that reduce catheters manipulation and therefore reduce the risk of embolism and the use of local anaesthesia instead of general anaesthesia for clinical monitoring (pain). Our observation of nMARQ efficacy and safety in PAF and PsAF suggested that the catheter technology may be a promising alternative to conventional point-by-point AF ablation and other catheter technologies when used carefully and support its future development to overcome the serious concerns associated with its application as reported by other studies.

The main limitation of the third study was the inappropriate study design to evaluate a potential predictive value of CMR and EP findings at 3 months. Indeed, patients had benefited from offered repeated procedure. Given the high prevalence of PV reconnection, additional ablation was performed in the vast majority of patients. However, predicting patient outcome was not within the scope of the present study that focused on analysing the relationship between scar and PV reconnection. Another potential limitation was the technology used in conventional single electrode catheter that was based on impedance based method instead of contact force, which was associated with more complete ablation set[514]. Lastly, we acknowledge that the scar quantification using CMR still lacks validation, and that there was to our knowledge no automated method that outperforms segmentations by experts as remained the gold standard[515]. Therefore, this limits the implementation of the method in current practice.

Conclusion

The nMARQ circular multielectrode irrigated catheter was 3 times faster in isolation PVs, with shorter RF and procedure time. It was associated with fewer PV reconnection at 3 months. The circular catheter demonstrated encouraging results for rapid, effective and safe technique in PsAF, especially when guided by non-invasive mapping. The circular catheter could be used effectively and safely for CTI and linear lesions in addition to PVI, therefore, obviating the need for an additional catheter in the majority of patients. This catheter appeared to be safe with no major procedural complications in our study.

PV reconnection and scar gaps on CMR were prevalent at 3 months after successful PVI despite clinical recurrence. While both scar burden and scar gaps extent on CMR correlate closely to the extent of PV reconnection, CMR performance to locate PV reconnection sites remained limited because of missed PV reconnection. Therefore, CMR lacks sensitivity to detect relevant gaps on sites showing pre-existing fibrosis. last, besides the dramatic reduction, in procedure duration, the use of circular multielectrode catheters was associated with higher scar burden, fewer and smaller gaps, fewer PV reconnection after PVI, and lower need for additional ablation to complete the lesion during repeated procedure. Overall, the circular multielectrode irrigated mapping and ablation catheter (nMARQ) was effective in treating PAF and PsAF, carrying the advantage for non-PV sites ablation and linear ablation access compared to other catheter technologies. NMARQ had the advantage of irrigation when compared to PVAC, the adaptation of energy settings and energy delivery. NMARQ is safe when it is used under local anaesthesia for clinical monitoring and energy setting adaptation. In addition, the circular catheter was associated with higher scar burden, fewer scar gaps, and fewer reconnected veins on CMR after PVI. PV reconnection was common, even in the absence of AF recurrence, and localizing reconnection site by CMR is not the best strategy, while quantifying the degree of reconnection might be more appropriate and accessible aim. Further studies may be required to evaluate the catheter energy setting technology and randomized comparison to evaluate the safety under local anaesthesia versus general anaesthesia.

Last but lost least, the use of CMR in electrophysiology is evolving. Interventional magnetic resonance imaging is the future aspect. Magnetic resonance (MR) guidance in electrophysiology (EP) procedures, combined with the avoidance of radiation exposure, offers the potential for arrhythmia substrate identification, improved procedural guidance and real-time ablation assessment of lesion formation. Accurate device tracking techniques were developed to offer an interface similar to electroanatomic mapping platforms, and MR-compatible EP equipment continues to be developed. However, the environment can present challenges and the cost is expensive[516].

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Pour chaque fin il y a toujours un nouveau départ.

Le petit prince