# Nouvelles perspectives diagnostiques et thérapeutiques dans la prise en charge rythmologique des patients en situation d'insuffisance cardiaque

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# THÈSE

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# Nouvelles perspectives diagnostiques et thérapeutiques dans la prise en charge rythmologique des patients en situation d'insuffisance cardiaque.


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## ABBREVIATIONS FRANCAISES

**AA** : anti-aldostérone

**AC :** ablation par cathéter

**ARA2** : antagoniste des récepteur de l'angiotensine de type II

**CEA :** cartographie électroanatomique

**CMD** : cardiomyopathie dilatée

**DAI** : défibrillateur automatique implantable

**DAI-RC** : défibrillateur automatique implantable de resynchronisation cardiaque

**DD** : dysfonction diastolique

**ECG** : électrocardiogramme

**FA** : fibrillation auriculaire

**FEVG** : fraction d'éjection du ventricule gauche

**FEVG-2D** : FEVG déterminée par échocardiographie bidimensionnelle

**FEVG-IRM** : FEVG déterminée par imagerie par résonance magnétique

**HTA** : hypertension artérielle

**HVG** : hypertrophie ventriculaire gauche

**IAH** : index apnées hypopnées

**IEC** : inhibiteurs de l'enzyme de conversion

**IC** : insuffisance cardiaque

**IC-FEm** : IC à FEVG modérément altérée

**IC-FEp** : IC à FEVG préservée

**IC-FEr** : IC à FEVG réduite

**IC 95%** : intervalle de confiance à 95%

**IRM** : imagerie par résonance magnétique

**IVP** : isolation des veines pulmonaires

**MS** : mort subite

**OR :** odds ratio

**PM** : pacemaker

**PM-RC** : PM de resynchronisation cardiaque

**PPC** : pression positive continue

**PSG** : polysomnographie

**PV** : polygraphie ventilatoire

**RC** : resynchronisation cardiaque

**RDI** : respiratory disturbance index

**RDIm** : RDI moyen

**RF** : radiofréquence

**RT** : rehaussement tardif

**SAS** : syndrome d'apnée du sommeil

**TA** : tachycardie atriale

**UHD** : ultra-haute densité

## ABBREVIATIONS ANGLAISES

**ACSS** : attended cardiorespiratory sleep study

**ACT** : activated clotting time

**ADT**: appropriate device therapy

**AF**, **AFib**: atrial fibrillation

**AHI** : apnea hypopnea index

**AT** : atrial tachycardia

**AUC** : area under the curve

**BMI :** body mass index

**CA:** catheter ablation

**CFAE:** complex fractionated atrial electrograms

**CI :** confidence interval

**CKD** : chronic kidney disease

**CMR** : cardiac magnetic resonance

**CMR-LVEF** : left ventricular ejection fraction measured with cardiac magnetic resonance imaging

**CPAP** : continuous positive airway pressure

**CRT** : cardiac resynchronization therapy

**DD :** diastolic dysfunction

**Ea** : early diastolic velocity

**ECG** : electrocardiogram

**e-CRF** : electronic case report forms

**HF** : heart failure

**HFpEF** : heart failure with preserved ejection fraction

**HFrEF** : HF patients with reduced LVEF

**HR** : hazard ratio

**ICC :** intraclass correlation coefficient

**ICD** : implantable cardioverter defibrillator

**ICM** : ischemic cardiomyopathy

**LA** : left atrium

**LBBB** : left-bundle branch block

**LGE** : late gadolinium enhancement

**LVEF** : left ventricular ejection fraction

**NPV** : negative predictive value

**NICM** : nonischemic cardiomyopathy

**NYHA** : New York Heart Association

**OR:** odds ratio

**PM** : pacemaker

**PPV** : positive predictive value

**PSG** : polysomnography

**PVI** : pulmonary veins isolation

**RA** : right atrium

**RDI** : respiratory disturbance index

**RF** : radio-frequency

**ROC** : receiver operating characteristic

**SA** : sleep apnea

**SAM** : sleep apnea monitoring

**Se** : sensibility

**Sp** : specificity

**SD** : standard deviation

**TDI** : tissular doppler imaging

**TTE** : transthoracic echocardiography

**UHD** : ultra-high-density

**2DE** : two-dimensional transthoracic echocardiography

**2D-LVEF** : left ventricular ejection fraction measured by two-dimensional transthoracic echocardiography

**3D**: three-dimensional

# INTRODUCTION

Après quelques généralités et rappels sur les différents types d'insuffisance cardiaque (IC) aujourd'hui décrits, nous aborderons les comorbidités associées, et plus particulièrement le syndrome d'apnée du sommeil (SAS) et la fibrillation auriculaire (FA), puis la prise en charge de l'IC d'un point de vue rythmologique, enfin certaines limites actuelles et questions non résolues qui serviront de point de départ aux différents travaux de cette thèse.

## 1. Généralités sur l'insuffisance cardiaque en 2019

L'IC est un syndrome clinique qui résulte d'anomalies myocardiques très variées aboutissant à une diminution du débit cardiaque. Elle reflète des situations cliniques très différentes, de par leur fondement physiopathologique, leur présentation et leur prise en charge. De façon globale, l'IC touche actuellement entre 1 et 2% de la population adulte dans les pays dits développés, avec une prévalence qui augmente avec l'âge pour atteindre plus de 10% chez les plus de 70 ans. (1) Avant les années 1990, qui ont vu naitre la prise en charge moderne de l'IC, 60 à 70% des patients mourraient dans les cinq années suivant le diagnostic.

De nombreux progrès ont été faits dans la prise en charge de l'IC, notamment basés sur les résultats des grands essais thérapeutiques menés dans le cadre l'IC associée à une fraction d'éjection du ventricule gauche (FEVG) altérée. L'avènement de différentes molécules a transformé le pronostic de cette maladie. Il s'agit des béta-bloquants, des inhibiteurs de l'enzyme de conversion (IEC), des anti-aldostérones (AA), des bloqueurs du courant If, et plus récemment de l'association d'antagonistes des récepteurs de l'angiotensine de type II (ARA2) et de la neprilysine. En parallèle du traitement médicamenteux, d'autres axes de la prise en charge, tels que le diagnostic plus précoce, la meilleure prise en charge des infarctus du myocarde, ainsi que le développement de la réadaptation cardiaque, ont également contribué à l'amélioration du pronostic des patients atteints d'IC. Enfin, les traitements dits « électriques » de l'IC, basés sur la prise en charge des troubles du rythme associés à l'IC, mais aussi sur l'amélioration de l'hémodynamique cardiaque, constituent aujourd'hui un autre

volet essentiel dans la prise en charge globale de l'IC. La survie après la première hospitalisation pour IC a ainsi augmenté de façon modeste mais significative au cours des 20 dernières années, passant chez l'homme de 1,33 années (intervalle de confiance à 95% [IC 95%] 1,17 à 1,50) en 1986 à 2,34 années (IC 95% 2,15 à 2,56) en 2002 (p<0,0001). (2)

## 2. Les différentes formes d'IC

Les étiologies de l'IC sont nombreuses et variables selon la région du monde, qu'il s'agisse de cardiomyopathies primitives associées à des anomalies génétiques, ou secondaires à l'athérosclérose, à un remodelage myocardique défavorable lié à une arythmie, ou à une maladie de système. D'abord limitée à l'IC à FEVG réduite (IC-FEr), l'amélioration des connaissances a permis d'individualiser d'autres formes d'IC : l'IC à FEVG préservée (IC-FEp), puis très récemment l'IC à FEVG modérément altérée (IC-FEm). (3)

L'IC-FEr, définie par une FEVG <40%, est la forme qui a été la plus étudiée depuis longtemps, dont la physiopathologie a été la mieux comprise, et pour laquelle les grands essais randomisés ont montré le bénéfice sur la morbi-mortalité des traitements évoqués précédemment. La maladie coronaire est en cause dans environ deux tiers des cas, associée à l'hypertension artérielle (HTA) et au diabète. Les autres causes sont les cardiomyopathies dilatées (CMD) pouvant être d'origine génétique, secondaires à des infections, des toxiques (alcool ou autres stupéfiants), des maladies de surcharge, des chimiothérapies cardiotoxiques, des maladies auto-immunes, des pathologies endocrines, ou enfin dans le cadre de la cardiomyopathie du péri-partum. (4) L'altération et/ou la nécrose des cardiomyocytes et les modifications de la matrice extra-cellulaire aboutissent à un remodelage pathologique ventriculaire conduisant à une dilatation, et à une réduction de la fonction contractile. Ces phénomènes vont s'aggraver avec le temps, par progression de la pathologie initiale mais aussi en raison d'une réponse systémique neuro-hormonale à la dégradation de la fonction systolique. En effet, l'activation du système rénine-angiotensine-aldostérone et du système neurovégétatif sympathique vont entraîner des dommages myocardiques supplémentaires mais aussi d'autres effets délétères, notamment vasculaires, ainsi qu'au niveau d'autres

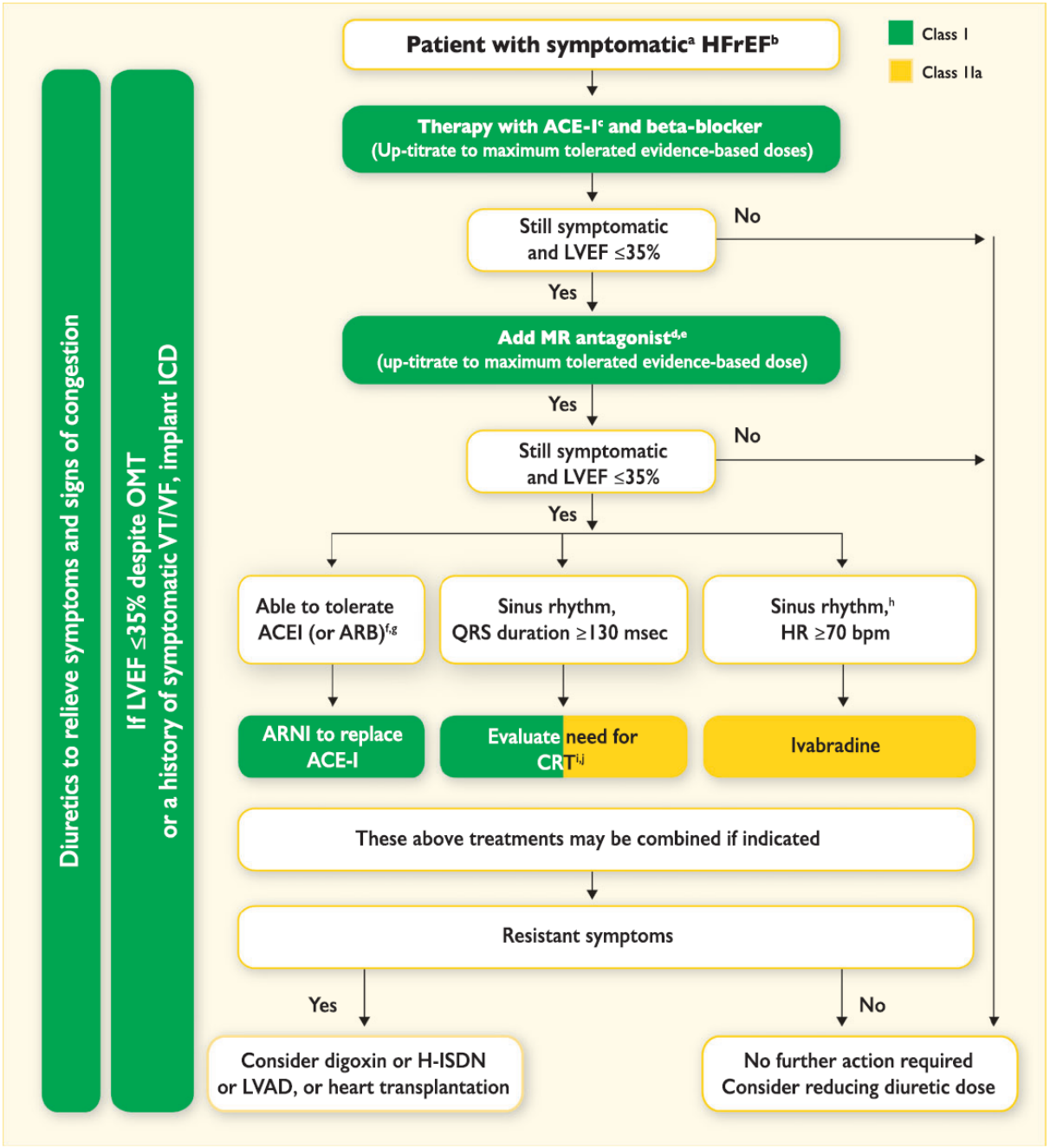
organes (foie, rein, muscles, poumons), conduisant à l'installation d'un cercle vicieux et rendant compte des complications qui émaillent l'évolution des patients. (5) La stratégie thérapeutique basée sur les résultats de nombreuses études randomisées est désormais bien codifiée et permet une prise en charge par étapes des patients présentant une IC-FEr (Figure 1).

L'IC à fonction systolique non altérée n'a été étudiée de façon spécifique que récemment, bien qu'elle soit en cause dans près de la moitié des cas d'IC. La définition de ce syndrome a varié au cours des dernières années, essentiellement en ce qui concerne les anomalies échographiques associées aux signes cliniques d'IC. Initialement, les experts opposaient l'IC systolique (FEVG<35-40%) et l'IC diastolique, cette dernière associant une FEVG préservée (>40-50%) sans limite basse précise à des anomalies de la fonction diastolique. (6) Puis la notion d'IC-FEp est apparue, basée sur une FEVG ≥50%, ce qui laissait une zone grise de FEVG entre 35-40% et 50% qu'il était difficile d'inclure dans l'un des deux syndromes définis. Finalement, l'IC-FEm, définie par une FEVG comprise entre 40 et 49%, est apparue dans les recommandations européennes de 2016, afin d'individualiser cette situation particulière dont les mécanismes et le pronostic semblent intermédiaires. (3)

Les étiologies et l'épidémiologie de ces syndromes semblent différentes de celles de l'IC-FEr, touchant des patients plus âgés, plus souvent des femmes et obèses, avec une histoire plus fréquente d'HTA et de fibrillation auriculaire (FA) (4). La mortalité à un an des patients avec une IC-FEp est inférieure à celle des patients dont la FEVG est altérée, celle des patients à IC-FEm est intermédiaire. Ces syndromes cliniques sont souvent plus difficiles à diagnostiquer car les signes et les symptômes sont parfois moins spécifiques qu'en cas d'IC-FEr. Les critères retenus sont l'association de signes/symptômes d'IC, associés à une FEVG entre 40 et 49% pour l'IC-FEm ou >50% pour l'IC-FEp, une élévation des peptides natriurétiques, et au moins une anomalie échographique parmi l'hypertrophie ventriculaire gauche (HVG), la dilatation de l'oreillette gauche et une altération de la fonction diastolique.

**Figure 1 : Algorithme thérapeutique d'un patient atteint d'IC-FEr symptomatique**

La couleur verte correspond à une recommandation de classe 1, la couleur jaune à une recommandation de classe 2. ACE-I : inhibiteur de l'enzyme de conversion ; ARB : antagonistes des récepteurs de type II de l'angiotensine ; ARNi : antagonistes des récepteurs de l'angiotensine de type 2 et de la néprilysine ; CRT : resynchronisation cardiaque ; H-ISDN : hydralazine dinitrate isosorbide ; HFrEF : IC-FEr ; HR : fréquence cardiaque ; ICD : défibrillateur cardiaque implantable ; LVAD : dispositif d'assistance ventriculaire gauche ; LVEF : FEVG ; OMT : traitement médical optimal ; VT/VF : fibrillation/tachycardie ventriculaire. Reproduite à partir des Recommandations 2016 de la Société Européenne de Cardiologie pour le diagnostic et le traitement de l'insuffisance cardiaque aigue et chronique. (3)



Il apparaît également que l'IC-FEp est un syndrome très hétérogène regroupant des phénotypes de patients et des comorbidités variées. (7) La physiopathologie est complexe et les mécanismes en cause sont liés, à la fois à des anomalies de la fonction diastolique du ventricule gauche, de la matrice extracellulaire, des phénomènes de stress oxydatif, et inflammatoires. La fonction systolique est également souvent anormale, même si la FEVG est peu altérée. (8) La dysfonction diastolique (DD) semble être au cœur des mécanismes conduisant à l'apparition de signes d'IC. Il s'agit d'une altération du remplissage ventriculaire associée à une élévation des pressions de remplissage. Différents mécanismes vont concourir à rendre le myocarde plus rigide, que ce soit au niveau des cardiomyocytes eux-mêmes ou au niveau de la matrice extra-cellulaire. On évoque des modifications des isomères de la titine avec un déséquilibre vers l'isoforme plus rigide en cas de DD, des anomalies des courants ioniques entraînant une surcharge calcique intra-cellulaire, ou encore des modifications de la sensibilité au calcium du myofilament par des anomalies de la protéine C liant la myosine, mais aussi les phénomènes de fibrose associée à l'HTA et à la sénescence avec des modifications du collagène extra-cellulaire. (9) Certaines anomalies participant à la DD sont probablement la conséquence de modifications neuro-hormonales. Parmi elles, l'hyperaldostéronisme, qu'il soit primaire ou secondaire, est associé à une HVG et une dégradation des paramètres de la fonction diastolique en échographie, alors qu'une altération de la fonction systolique, le plus souvent modeste, n'existe qu'en cas d'hyperaldostéronisme primitif. (10) L'élévation progressive des pressions pulmonaires, secondaire à l'augmentation des pressions de remplissage gauches, mais également à des anomalies de la vascularisation pulmonaire avec une dysfonction endothéliale et une rigidification artérielle, va participer à la dégradation de la tolérance à l'effort et à l'apparition de signes d'IC. (7)

## 3. Les comorbidités aggravant l'IC

Un des principaux problèmes dans la prise en charge des patients en IC est l'implication de nombreuses comorbidités cardiaques ou non cardiaques, qui vont aggraver leur pronostic. Une large étude transversale, publiée dès 2003, sur 122 630 bénéficiaires de Medicare âgés

de 65 ans et plus, avait mis en évidence la prévalence élevée de comorbidités non cardiaques, ainsi que leur association avec les hospitalisations, liées à l'IC ou pour autre cause, et la mortalité. Ces pathologies associées étaient l'HTA, la broncho-pneumopathie chronique obstructive, l'insuffisance rénale, le diabète, la dépression et les autres maladies respiratoires distales. (11) La maladie coronaire, la FA, l'obésité, la dyslipidémie, la dénutrition, les cancers, les maladies neuro-vasculaires, les dyskaliémies et plus récemment, la carence martiale et les troubles ventilatoires nocturnes ont été reconnus comme des co-facteurs fréquents et aggravants de l'IC nécessitant une prise en charge spécifique. (3,12,13) L'importance de ces co-morbidités est d'autant plus marquée chez les patients atteints d'IC-FEp, pour lesquels ces facteurs associés constituent des tableaux phénotypiques différents, dont l'identification est importante pour orienter la stratégie thérapeutique.

### *3.1 Le syndrome d'apnée du sommeil*

Parmi ces pathologies associées, le SAS, qui est le plus souvent de forme obstructive est associé à une augmentation de la mortalité cardiovasculaire mais aussi globale. Il favorise l'HTA, les troubles du rythme, l'athérosclérose et ainsi la survenue d'infarctus du myocarde ou d'accident vasculaire cérébral, mais est également associé à une surmortalité par cancer. (14,15) Le SAS s'accompagne également souvent d'un hyperaldostéronisme. Il a été mis en évidence une relation entre la présence d'un hyperaldostéronisme et l'existence d'un SAS chez des patients souffrant d'HTA résistante, et que la sévérité du SAS était corrélée au niveau d'aldostérone plasmatique. (16) De même, une étude portant sur plus de 3000 patients hypertendus d'ethnies différentes a retrouvé une prévalence significativement plus élevée de SAS en cas d'hyperaldostéronisme, après contrôle des autres facteurs de risque de SAS. (17) Une autre étude, cette fois menée chez des patients présentant un SAS obstructif, a montré que les taux d'aldostérone plasmatique étaient plus élevés que chez les patients contrôles, et que le traitement du SAS permettait de diminuer l'aldostéronémie. (18) Il est probable que l'hyperaldostéronisme associé au SAS constitue une des voies de participation de ce trouble du sommeil aux pathologies cardio-vasculaires, notamment à l'aggravation de l'IC.

La prévalence du SAS est élevée et augmente avec l'âge, atteignant environ 5-7% de la population générale, et jusqu'à 15% ou plus après 70 ans. (19) Ces chiffres sont de plus probablement sous-estimés, compte tenu du caractère souvent pauci-symptomatique de cette pathologie et de signes d'appel peu spécifiques. Il est plus fréquent chez les hommes, les patients obèses, atteints de diabète de type 2 ou de syndrome métabolique. (20) Le diagnostic du SAS associe la présence d'une somnolence diurne excessive ou d'autres symptômes (ronflements, suffocation nocturne, difficulté de concentration, asthénie, nycturie) à un critère polysomnographique, l'index apnées hypopnées (IAH), correspondant au nombre d'apnées et d'hypopnées par heure de sommeil, supérieur ou égal à cinq. (21) Le SAS obstructif est lié à la présence d'une obstruction intermittente et répétée des voies aériennes supérieures pendant le sommeil, favorisée par des anomalies anatomiques (rétrognathie, macroglossie etc.) ou l'obésité. Le SAS d'origine centrale se caractérise par la survenue répétée d'arrêts complets de tout effort respiratoire, liés à une anomalie de la commande ventilatoire que l'on observe par exemple en cas d'atteinte du tronc cérébral ou d'IC sévère. Dans le cas de l'IC, le SAS est souvent mixte, la composante centrale étant liée à une instabilité de ventilation au cours du sommeil. Cette respiration périodique correspond à une succession de phases d'hyperventilation puis d'hypoventilation aboutissant à l'apnée. Une petite augmentation de la pression partielle en $CO_2$ nocturne provoque une hyperventilation exagérée et une chute progressive de la $PaCO_2$ sous un certain seuil, déclenchant une hypoventilation par inhibition des commandes centrales de ventilation. Le retard circulatoire provoque un retard de réponse des chémorécepteurs, aboutissant à l'apnée centrale. L'hypercapnie qui en résulte provoque alors un réveil neurologique partiel et un nouveau cycle d'hyperpnée, etc.

Le traitement par pression positive continue (PPC) est efficace dans le SAS obstructif et permet d'améliorer la prise en charge des comorbidités associées telles que l'HTA ou les arythmies. Il est indiqué en France dans les formes sévères (IAH≥30/h), ou dans les formes modérées (IAH entre 15 et 30/h) associées à une maladie cardiovasculaire, et est recommandé dans la stratégie de prise en charge globale des patients avec IC. (3,13)

Cependant, il n'est pas toujours efficace en cas de SAS central et l'utilisation de la ventilation servo-adaptée chez des patients IC-FEr a été associée à une surmortalité totale et cardiovasculaire dans l'étude SERVE-HF. (22)

### *3.2 La fibrillation auriculaire*

La FA est le trouble du rythme le plus souvent associé à l'IC. Elle en est une fréquente complication car l'élévation des pressions de remplissage secondaire à l'IC favorise le remodelage atrial conduisant au déclenchement et la perpétuation de la FA. Dans certains cas de cardiomyopathie rythmique, c'est la FA elle-même, généralement à cadence ventriculaire élevée, qui est à l'origine de la dégradation de la fonction cardiaque. Ces formes d'IC secondaires à la survenue d'une FA sont généralement de plutôt bon pronostic. (23) En revanche, l'apparition d'une FA chez un patient porteur d'une IC est un facteur pronostique péjoratif, traduisant l'aggravation de la pathologie sous-jacente, et entraînant une dégradation supplémentaire de la fonction cardiaque. Elle marque souvent un tournant évolutif dans la maladie, et est associée à une augmentation des hospitalisations et de la mortalité, qu'il s'agisse d'IC-FEr ou d'IC-FEp. (24,25) Dans le cas particulier de l'IC-FEp, la FA est aussi particulièrement fréquente, notamment dans le phénotype de patients âgés, chez lesquels la FA, l'anémie, les pathologies respiratoires obstructives et la fragilité rendent la prise en charge de l'IC particulièrement difficile. (26) De plus, le remodelage atrial qui conduit à la survenue de la FA diffère entre l'IC-FEr et l'IC-FEp. Dans la première, la principale anomalie est la dilatation atriale, alors que dans l'IC-FEp, l'oreillette gauche est moins dilatée, mais plus rigide, avec une élévation de la pression maximale et de la pulsatilité, ces anomalies semblant associées à une incidence plus importante de FA. (27)

## 4. La prise en charge de l'insuffisance cardiaque du point de vue rythmologique

### *4.1 La stimulation cardiaque conventionnelle*

La mise en place d'un stimulateur cardiaque ou pacemaker (PM) dans un contexte d'IC relève des indications classiques de la stimulation cardiaque : bloc auriculo-ventriculaire de haut

degré (type III et type II mobitz 2), dysfonction sinusale symptomatique, bradyarythmie. Il existe néanmoins des particularités liées à la situation d'IC. Des observations anciennes ont mis en évidence une diminution de la performance hémodynamique cardiaque en cas de stimulation ventriculaire droite comparée à une stimulation biventriculaire, expliquée par un asynchronisme mécanique secondaire à l'activation séquentielle des deux ventricules. (28) Les études menées chez des patients présentant une indication de stimulation cardiaque, sans IC associée, ont également montré un impact hémodynamique négatif de la stimulation ventriculaire droite. (29) De ce fait, il est plutôt préférable de mettre en place un PM double chambre permettant le maintien de la synchronisation atrioventriculaire et de limiter le pourcentage de stimulation ventriculaire, même chez les patients ne présentant pas d'altération de la fonction cardiaque. Enfin, plusieurs équipes ont mis en évidence l'aggravation de l'asynchronisme mécanique existant en cas d'altération de la FEVG par la stimulation cardiaque droite, pouvant être corrigé par la stimulation biventriculaire. (30,31) Celle-ci doit donc être envisagée en cas d'indication de stimulation ventriculaire en présence d'une IC-FEr.

Il existe également des indications spécifiques de stimulation dans certaines étiologies d'IC, par exemple pour limiter l'obstacle hémodynamique à l'éjection en cas de cardiomyopathie hypertrophique obstructive, ou à titre préventif en raison de l'évolution connue mais peu prévisible vers des troubles de la conduction auriculo-ventriculaire de haut degré, comme dans les laminopathies ou la sarcoïdose. Enfin, l'intérêt du traitement beta-bloquant étant établi en cas d'IC-FEr en rythme sinusal, la question se pose en cas de bradycardie excessive ou de pauses fréquentes et symptomatiques, entre la réduction de dose voire l'arrêt du traitement ou la stimulation biventriculaire. Cependant, la stimulation cardiaque pour la seule indication d'initier ou maintenir un traitement béta-bloquant n'est pas recommandée. (3)

### *4.2 La prévention de la mort subite*

Environ 30% des patients en situation d'IC décèdent brutalement, surtout parmi ceux qui sont peu ou modérément symptomatiques. La mort subite (MS) rythmique par troubles du rythme

ventriculaires graves est au premier plan. (32) Les défibrillateurs automatiques implantables (DAI), depuis leurs premières utilisations il y a plus de trente ans, ont permis diminuer de façon significative la mortalité rythmique des patients en IC. Les premiers travaux sur la prévention secondaire ont permis de clairement poser les indications d'implantation en cas de MS récupérée ou de troubles du rythme ventriculaires symptomatiques, qu'il existe ou pas une cardiomyopathie sous-jacente et en l'absence de cause aigue réversible. (33) Puis, les grands essais randomisés des années 2000 (30–35) ont mis en évidence le bénéfice du DAI pour la prévention primaire de la MS chez des patients présentant une IC-FEr, en diminuant celle-ci et en améliorant la survie globale. (34–39) L'implantation d'un DAI est actuellement recommandée pour les patients en stade II et III de la New York Heart Association (NYHA), ayant une FEVG altérée ≤35% malgré un traitement médicamenteux optimal pendant au moins trois mois et ayant une espérance de vie d'au moins un an avec un statut fonctionnel correct. (3) La prévention de la MS chez les patients présentant une IC à FEVG préservée n'est quant à elle pas bien codifiée actuellement.

### *4.3 La resynchronisation cardiaque*

Le bénéfice de la stimulation biventriculaire, par rapport à la stimulation ventriculaire droite exclusive, a déjà été évoqué précédemment en cas d'indication conventionnelle de stimulation cardiaque. La première expérience clinique de « resynchronisation » en dehors d'un contexte de stimulation cardiaque a été réalisée en France par Serge Cazeau en 1994, chez un patient en IC stade IV de la NYHA. (40) Le rationnel de la resynchronisation cardiaque (RC) repose sur l'existence d'un asynchronisme cardiaque au cours de l'IC-FEr, qui peut être auriculo-ventriculaire, interventriculaire et/ou intraventriculaire gauche. Les mécanismes d'action de la RC sont multiples et aboutissent à un phénomène de remodelage inverse et à une amélioration des différents paramètres hémodynamiques. (41) De nombreux progrès techniques, au niveau des dispositifs et des techniques d'implantations, ont permis de simplifier les procédures et d'en diminuer la morbidité, en permettant notamment la stimulation épicardique du ventricule gauche par voie endocavitaire via le sinus coronaire, en évitant ainsi le recours à une

thoracotomie chirurgicale. Plusieurs études randomisées ont montré une amélioration des symptômes, une réduction des hospitalisations mais aussi de la mortalité grâce aux stimulateurs et défibrillateurs de RC. (42–45) La mise en place d'une RC est à envisager pour les patients éligibles ayant une FEVG altérée inférieure ou égale à 35%, restant symptomatiques malgré au moins trois mois de traitement médical optimal, et ayant une espérance de vie supérieure à un an avec un bon statut fonctionnel. Les critères essentiels de réponse à la RC sont la durée et l'aspect de retard gauche des QRS. Les recommandations ont ainsi évolué, et aujourd'hui le grade le plus élevé de recommandation s'adresse aux patients ayant un retard gauche et des QRS ≥150ms. Les patients en FA ont été moins étudiés et semblent moins répondre ceux en rythme sinusal, cependant la RC est également proposée chez eux, en s'assurant d'un bon contrôle de la fréquence cardiaque permettant un pourcentage de stimulation biventriculaire optimal. (3)

Il existe des stimulateurs (PM-RC) et des défibrillateurs de RC (DAI-RC), ces derniers associant à la stimulation cardiaque biventriculaire la possibilité de délivrer des thérapies anti-tachycardiques. L'intérêt théorique d'implanter un DAI-RC plutôt qu'un PM-RC, pour améliorer davantage la survie en réduisant la MS, n'a jamais été clairement démontré par les études menées jusqu'à présent. Compte-tenu de la prévalence plus élevée de la MS chez les patients plus jeunes et modérément symptomatique, du risque accru de complications chez les porteurs de défibrillateur (fragilité de l'électrode de défibrillation, thérapies inappropriées), du coût plus élevé de ces dispositifs, il est aujourd'hui préconisé de fonder le choix entre un PM-RC et un DAI-RC au cas par cas selon l'âge, les comorbidités associées, le stade NYHA, le statut fonctionnel mais aussi le souhait du patient.

### *4.4 Le traitement interventionnel des arythmies*

Nous avons précédemment rappelé, que la FA était le trouble du rythme le plus souvent associé à l'IC, et qu'elle en aggravait le pronostic, que la FEVG soit altérée ou préservée. De nombreux traitement de l'IC ont montré une diminution de l'incidence de la FA, probablement par le biais d'une amélioration hémodynamique, que ce soit les bloqueurs du système rénine-

angiotensine-aldostérone ou les béta-bloquants. Le premier axe du traitement en cas de survenue de FA récente chez un patient IC est le contrôle de la fréquence par béta-bloquants ou digitaliques, et, en cas de mauvaise tolérance, une cardioversion, qu'elle soit médicamenteuse ou électrique. Au long cours, la stratégie de contrôle du rythme par traitement antiarythmique, bien que couramment utilisée, n'avait jusqu'à présent pas montré de bénéfice supplémentaire par rapport au contrôle de la fréquence en cas d'IC. (46)

Cependant, le mise au point et le développement des techniques interventionnelles, dites d'ablation par cathéter (AC) ont montré au cours de la dernière décennie des résultats de plus en plus prometteurs chez les patients avec IC-FEr. Après avoir rapporté la faisabilité de l'isolation des veines pulmonaires (IVP) chez les patients avec une IC-FEr, les études ont mis en évidence une amélioration des symptômes, un remodelage échographique favorable et une réduction des hospitalisations après l'AC. Il s'agissait de procédures toutes basées sur une IVP antrale, plus ou moins associée à des ablations complémentaires, linéaires ou basées sur les potentiels fragmentés. (47–50) La technique la plus utilisée pour réaliser ces interventions est la radiofréquence (RF) point par point, qui est la seule à permettre à la fois le traitement des foyers des veines pulmonaires et celui du substrat. Il existe d'autres énergies et méthodes d'applications pour l'IVP, par exemple la cryoablation au moyen d'un ballon, qui permet un traitement dit « one-shot », en une application par veine à isoler. Une étude allemande très récente, a rapporté la faisabilité, et les résultats similaires sur les récurrences de FA, de l'IVP par cryoablation chez des patients avec une FEVG ≤40%, associée également à une amélioration fonctionnelle significative, par rapport à des patients contrôles. (51) Enfin, l'étude CASTLE-AF, publiée en 2018, a pour la première fois montré une réduction d'un critère combiné associant la mortalité toute cause et les hospitalisations pour IC chez des patients ayant une IC-FEr (≤35%) en stade NYHA II, III ou IV, grâce à l'AC, comparée au traitement médical. La mortalité toute cause et cardiovasculaire ont également été diminuées par l'ablation mais il s'agissait de critères secondaires. (52)

## 5. Les limites actuelles de ces traitements

Malgré les considérables progrès réalisés ces 30 dernières années, à la fois dans la prévention, le diagnostic et le traitement des patients en situation d'IC, cette pathologie reste associée à une morbi-mortalité élevée. Un certain nombre de questions restent aujourd'hui non résolues, notamment dans la prise en charge des arythmies au sens large, et font l'objet de recherches en cours ou à venir. Nous en avons ici retenu quatre, qui constituent le point de départ des quatre travaux de cette thèse.

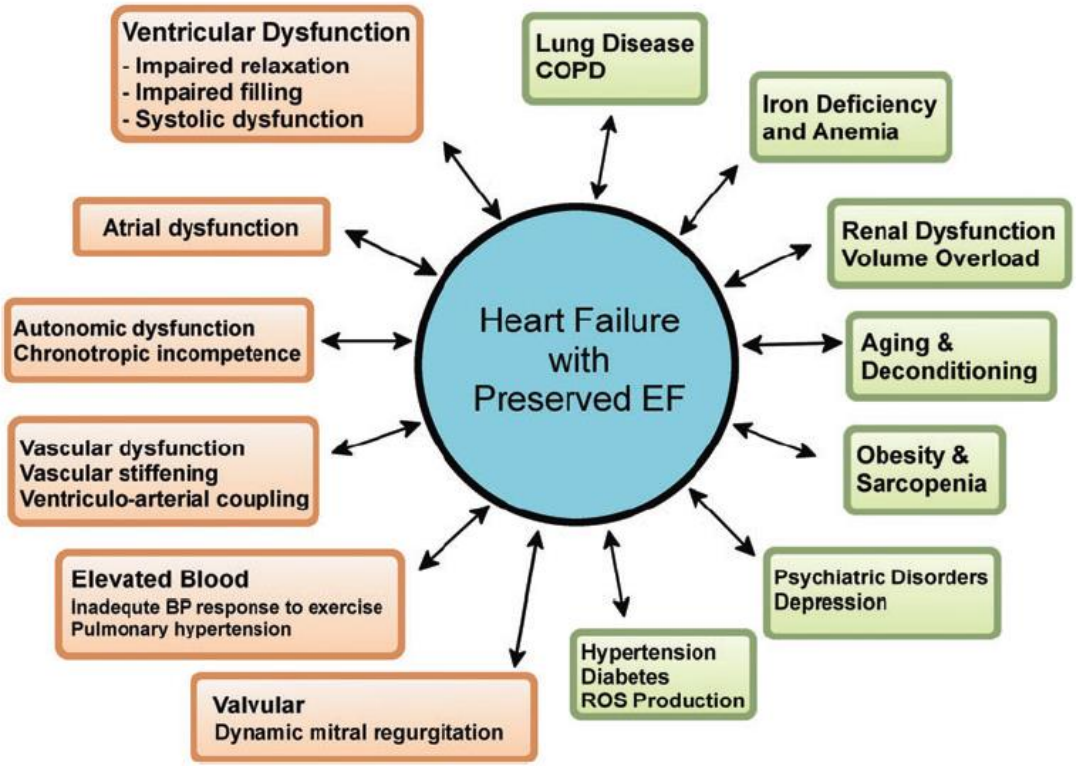
### *5.1 La difficulté de traitement de l'insuffisance cardiaque à fraction d'éjection préservée*

La prise en charge des patients atteints d'IC-FEm/p est plus délicate et beaucoup moins codifiée. De nombreuses études ont été menées sans permettre d'avoir des preuves solides sur les bénéfices des molécules utilisées avec succès dans l'IC-FEr sur la morbi-mortalité associée à l'IC-FEp. L'IC-FEm ayant été individualisée très récemment, aucune étude dédiée n'a encore été publiée et les seules données dans cette catégorie de patients proviennent des analyses post-hoc des études sur les autres formes d'IC. Aucun des essais menés chez des patients avec IC-FEp, que ce soit avec les beta-bloquants, les IEC ; les ARA2 ou les AA, n'a réussi à montrer un bénéfice sur la mortalité. Seule l'étude SENIORS, en 2005, avait montré une diminution d'un critère associant mortalité toute cause et hospitalisations cardiovasculaires avec un traitement par nébivolol, chez des patients souffrant d'IC et âgés de 70 ans et plus, que la FEVG soit altérée ou non. (53) Les diurétiques ont quant à eux montré un bénéfice sur les symptômes liés à la congestion pulmonaire. (54) Le candésartan, au travers des analyses des programmes CHARM et CHARM-PRESERVED, semble améliorer les symptômes, avec une réduction de la classe NYHA, et réduire les hospitalisations. (55,56) De même, les AA pourraient également limiter les réhospitalisations pour IC. L'étude TOPCAT était négative sur le critère composite primaire (mortalité cardiovasculaire, arrêt cardiaque récupéré, hospitalisations pour aggravation de l'IC) mais a montré une réduction des hospitalisations pour IC sous spironolactone (57). Son étude post-hoc, portant sur les

variations régionales des résultats, avait mis en évidence un bénéfice sur le critère primaire chez les patients du continent américain. (58)

**Figure 2 : Hétérogénéité de l'insuffisance cardiaque à fonction systolique préservée**

En rouge les anomalies physiopathologiques à l'origine des symptômes, en vert les comorbidités associées. BP : pression artérielle, COPD : bronchopneumopathie chronique obstructive, EF : fraction d'éjection, ROS : dérivés réactifs de l'Oxygène. Reproduite d'après Senni et al. (7)




Les preuves restant assez limitées, les seules recommandations en Europe pour la prise en charge de l'IC-FEp sont de traiter les comorbidités associées et d'utiliser des diurétiques pour améliorer les symptômes. Les recommandations américaines de 2017 suggèrent également, pour réduire les hospitalisations, l'utilisation des AA et des ARA2. Il s'agit de recommandations modestes de grade IIb, associées à un niveau de preuve B. (13) En faisant le parallèle avec les thérapies ciblées en cancérologie et en tenant compte du caractère très hétérogène des situations cliniques regroupées sous le terme IC-FEm/p, plusieurs auteurs proposent aujourd'hui, comme voie de développement, de cibler les différents phénotypes qui pourraient

répondre à une prise en charge plus spécifique : HTA, diabète, syndrome métabolique et obésité, hypertension pulmonaire, fibrose myocardique, ischémie, insuffisance rénale, déconditionnement et cachexie, troubles ventilatoires (Figure 2). (7) Parmi ces comorbidités, le SAS apparaît comme une cible importante, car il participe comme on l'a vu à de nombreux phénomènes physiopathologiques aggravants, ce d'autant que son diagnostic est difficile, les patients étant souvent peu symptomatiques, et les examens diagnostiques d'accès difficile. Pour cette raison, les nouveaux outils de dépistage du SAS, disponibles dans des prothèses cardiaques, peuvent peut-être améliorer la reconnaissance de cette pathologie chez des patients potentiellement à risque de développer un phénotype d'IC.

### *5.2 Les difficultés à prédire les évènements rythmiques et à sélectionner les patients relevant d'un défibrillateur prophylactique*

Les deux grands essais portant sur la prévention primaire de la MS, MADIT II et SCD-HEFT, ont montré une réduction significative du risque relatif de mortalité d'environ 30% grâce au DAI, chez des patients porteurs d'une IC-FEr symptomatique. (35,37) Néanmoins la réduction absolue de la mortalité était entre 5 et 7% selon les études, ce qui correspond à un nombre de patients à traiter de 14 à 20 pour éviter un décès. De plus, le taux annuel de chocs appropriés, c'est-à-dire délivrés par l'appareil pour convertir un trouble du rythme ventriculaire soutenu, était seulement de 5% par an. (37) En effet, la mortalité par MS rythmique, secondaire à un trouble du rythme ventriculaire grave, a tendance à diminuer avec l'évolution de la cardiopathie dans le temps, et la plupart des patients porteurs de DAI décèdent finalement d'IC terminale.

De plus, les complications et l'iatrogénie liées au DAI ne sont pas négligeables. Une méta-analyse des cinq études randomisées menées sur le DAI-RC a montré un taux de complications à 30 jours de 4% pour le groupe DAI, comparé à 18% dans le groupe DAI-RC, principalement des déplacements de sonde, des échecs d'implantation et des infections. (59) A plus long terme, les taux de complications restent élevés, comme l'a montré un registre prospectif canadien, qui rapportait des taux de réinterventions, hors remplacement pour usure,

à cinq ans supérieurs à 20% quel que soit le type de dispositif, les taux les plus élevés étant observés en cas de prévention primaire et pour les dispositifs de RC. (60)

Chez les patients ayant une cardiopathie sous-jacente, la fonction cardiaque et la capacité fonctionnelle sont directement associées à la mortalité totale et à la MS. C'est pourquoi la FEVG et le stade NYHA ont été les critères d'inclusion des études qui ont montré le bénéfice du DAI. Cependant, ces paramètres sont soumis à des variations de mesure importantes, qu'il s'agisse de la FEVG, selon la technique, les conditions de charge et l'opérateur, ou du stade NYHA dont l'appréciation est largement subjective. De plus, seuls 13% des MS surviennent chez des patients ayant une altération de la FEVG, la plupart survenant chez des individus sans maladie cardiaque connue (45% des MS) ou ayant une FEVG >40% (40% des MS), qui n'auraient donc pas été candidats à un DAI prophylactique. (61)

Une autre question a été soulevée récemment suite à la publication des résultats de l'étude DANISH, qui a évalué, à nouveau, le bénéfice du DAI prophylactique chez les patients porteurs d'une CMD associée à une FEVG <35%. En effet, les différents essais de prévention primaire n'avaient pas permis individuellement de prouver la supériorité du DAI par rapport au traitement médical dans cette population, et ce ne sont que les données groupées de ces études qui avaient permis d'aboutir aux recommandations du DAI prophylactique en cas de CMD. (62) Dans l'étude DANISH, le DAI prophylactique n'a pas montré de réduction de la mortalité globale, en dépit d'une réduction de la mortalité subite. La réduction de la mortalité globale était significative chez les patients de moins de 59 ans, alors qu'au contraire, la mortalité avait tendance à augmenter chez les plus de 68 ans. (63) Cet effet de l'âge était probablement lié à l'augmentation de la mortalité par IC terminale et non-cardiaque. Cependant, les recommandations n'ont aujourd'hui pas été modifiées. Il est uniquement proposé de considérer le fait de ne pas implanter de DAI chez un patient souffrant d'IC-FEr secondaire à une CMD, s'il est âgé de plus de 70 ans, en stade III-IV de la NYHA, avec des comorbidités non-cardiaques qui le rendent à risque de décéder d'autre chose que de MS rythmique. (64)

Il apparaît donc nécessaire d'améliorer la prédiction de la MS afin de mieux sélectionner les patients qui tireront réellement bénéfice d'un DAI prophylactique. De nombreuses pistes ont été étudiées : les anomalies de l'électrocardiogramme (ECG) traduisant l'instabilité électrique, comme l'alternance de ondes T ; les anomalies du système nerveux autonome explorées entre autres par le test du baroréflexe ; les polymorphismes génétiques ; l'évaluation de la dénervation sympathique cardiaque globale ou régionale par la scintigraphie au $^{123}$mIBG; la taille de la cicatrice en imagerie nucléaire mais aussi en imagerie par résonance magnétique (IRM). (61,65) D'autres équipes ont proposé des scores de prédiction, regroupant différents indices cliniques et paracliniques. (66,67) Ces approches ont toutes montré des résultats intéressants sur la prédiction des évènements rythmiques. C'est le cas, par exemple, de la scintigraphie au $^{123}$mIBG, avec l'étude ADMIRE-HF qui a montré qu'un rapport cardio-médiastinal de $^{123}$mIBG <1,6 améliorait la prédiction des décès et des évènements rythmiques par rapport à la FEVG seule. (68) Cependant, ces résultats restent limités, certaines de ces techniques sont soumises à des difficultés de reproductibilité des méthodes de mesure, et il n'existe pas aujourd'hui suffisamment de preuves pour recommander l'utilisation courante d'un de ces outils en pratique clinique. Seuls la FEVG et le stade NYHA apparaissent dans les recommandations les plus récentes sur la sélection des patients IC pour la prévention primaire de la MS, en dehors de certaines étiologies spécifiques, comme la cardiomyopathie hypertrophique ou la CMD associée à une laminopathie, pour lesquelles ils existent d'autres facteurs à prendre en compte.

### *5.3 Les questions non résolues de la resynchronisation*

Aujourd'hui, seule la combinaison du stade NYHA II ou III, avec une altération de la FEVG inférieure à 35% et un trouble conductif intra-ventriculaire sur l'ECG, de type bloc de branche gauche d'une durée supérieure ou égale à 130ms, est utilisée pour la sélection des patients pouvant bénéficier d'une RC. Cependant 30 à 35 % des patients implantés selon ces critères sont non répondeurs. Les autres paramètres évalués jusqu'à présent, surtout échographiques, bien que prometteurs, se sont tous révélés décevants dans les essais cliniques. (69) Certaines

données récentes suggèrent que l'allongement de l'intervalle PR sur l'ECG pourrait jouer un rôle dans la réponse à la RC, mais il manque des données cliniques prospectives permettant de les valider. (70) Comme nous l'avons évoqué précédemment, la réponse clinique à la RC chez les patients en FA reste également plus difficile à évaluer, ainsi que la nécessité d'y associer ou pas une ablation de la jonction nodo-hissienne.

D'autre part, l'IC est une maladie de la personne âgée, voire très âgée. La population des pays développés continue à vieillir et l'âge moyen au moment du premier diagnostic d'IC est de 75 ans. (71) La plupart des patients traités sont donc des octogénaires. Cependant, les preuves du bénéfice de la RC dans l'IC-FEr sont issues d'essais cliniques ayant inclus des patients dont l'âge moyen était 65 ans. (59) Dans ces études, les patients plus âgés ont été exclus ou très largement sous-représentés. Si 34% des participants de CARE-HF avaient 70 ans et plus, seulement 6.1% d'entre eux étaient âgés de plus de 80 ans, or c'est la seule étude dont la méthodologie a permis de prouver une réduction de la mortalité grâce à la RC. (43,72) Quelques travaux récents, la plupart rétrospectifs, ont eu tendance à montrer une faisabilité de la RC chez des patients âgés de plus de 70-80 ans, sans augmentation significative des complications, et associée à une amélioration des symptômes d'IC similaire à celle observée chez des patients plus jeunes. (73–75) Il manque cependant de preuves pour supporter l'utilisation de la RC chez ces patients plus fragiles, ayant souvent plus de comorbidités, avec un risque de complications plus important et un bénéfice plus incertain. La mortalité plus importante de cette population, souvent non cardiaque, mais aussi d'autres particularités liées à l'âge comme les troubles cognitifs, la perception de la qualité de vie ainsi que le rapport à la fin de vie, posent la question de l'intérêt de ces traitements invasifs, RC associée ou non à un DAI, après un certain âge.

### *5.4 Améliorer les résultats de l'ablation par cathéter chez les patients IC*

Si les données en faveur de l'AC de la FA dans les situations d'IC se sont multipliées ces dernières années, elles restent encore insuffisantes pour modifier les recommandations en profondeur, et proposer l'ablation de toutes les formes de FA au cours des différentes

situations d'IC, définies selon la fonction systolique. Malgré l'enthousiasme suscité au sein de la communauté rythmologique par les résultats de CASTLE-AF, les experts restent assez prudents quant à la place de l'ablation RF dans la prise en charge de la FA chez les patients avec IC. En effet, l'autre grande étude, comparant l'AC de la FA au traitement médical sur un critère associant mortalité, accident vasculaire, saignement majeur et arrêt cardiaque, attendue depuis plusieurs années et récemment terminée, CABANA, a rapporté un résultat négatif, même si le sous-groupe de patients avec IC avait toutefois tendance à améliorer le critère primaire (HR 0,61, IC 95% 0,35 à 1,08). (76,77) L'ablation de la FA paroxystique par IVP peut être envisagée chez les patients en IC, chez qui les épisodes d'arythmie sont responsables d'une aggravation symptomatique. En ce qui concerne l'ablation de la FA persistante, elle n'est proposée que chez les patients porteurs d'une IC-FEr et déjà appareillés (PM ou DAI +/- RC), si la FA est associée à une aggravation des symptômes et qu'une restauration du rythme sinusal est probable. (3,64)

Une des principales limites de l'AC dans la FA est le taux élevé de récidive, en particulier en cas de FA persistante, puisque près de 50% des patients récidivent après une procédure unique. (78) En cas de FA persistante de longue durée, le taux de maintien en rythme sinusal passe de 35% à un an à 17% à cinq ans. (79) De plus, les patients souffrant d'IC présentent un terrain particulièrement propice à la récidive et à la persistance de la FA. L'élévation chronique des pressions de remplissage, entrecoupée de poussées aigues, la régurgitation mitrale et les modifications neuro-hormonales associées à l'IC, vont favoriser la dilatation atriale, ainsi que son remodelage tissulaire et électrique. Les résultats de l'ablation dans les groupes les plus à risque restent donc à évaluer, par exemple en cas de dilatation importante de l'oreillette gauche, de cardiomyopathie hypertrophique ou d'IC-FEp.

De nouveaux outils technologiques sont régulièrement proposés par l'industrie afin d'améliorer les résultats de l'ablation. Il s'agit par exemple, des cathéters de contact permettant de monitorer l'efficacité et la sécurité des lésions délivrées, des systèmes de cartographie électroanatomiques (CEA) haute densité, de l'imagerie pour guider l'ablation, de nouvelles

énergies. Bien que des séries observationnelles rapportent des résultats intéressants, il n'y a pas eu de bénéfice prouvé dans des essais randomisés. (80) L'étude TOCCASTAR, par exemple, n'a pas montré de supériorité du cathéter de contact sur la récidive d'arythmie à 12 mois après une procédure d'IVP, au sein d'une population de 300 patients randomisés entre le cathéter de contact et le cathéter conventionnel. (81) D'autre part, les systèmes de CAE ont été proposés depuis un peu plus d'une dizaine d'années pour aider à la réalisation des procédures d'ablation de FA et autres tachycardies atriales (TA), en permettant la création d'un modèle anatomique tridimensionnel sur lequel peuvent être projetés les électrogrammes acquis selon un codage couleur lié à l'amplitude du signal électrique, ou à sa temporalité par rapport à une référence, mais aussi les points d'ablation, les cathéters en temps réel, avec également la possibilité de réaliser une fusion avec une imagerie pré-opératoire (scanner ou IRM). Les publications concernant ces systèmes, qu'il s'agisse du Carto™ (Biosense Webster Inc., Irvine, CA, USA) ou de l'Ensite™ (Abbott, Chicago, IL, USA), ont montré de façon reproductible leur capacité à réduire de façon significative les durées de fluoroscopie, malgré une courbe d'apprentissage nécessaire à l'utilisation de ces systèmes. Cependant, les résultats étaient plus mitigés sur la réduction des durées de procédure, ainsi que sur l'amélioration de l'efficacité de l'AC, évaluée par les récurrences. (82–85) En ce qui concerne les patients atteints d'IC, les enjeux de l'utilisation de ces nouveaux outils technologiques sont multiples, à la fois diminuer le risque de récidive d'arythmie, améliorer le pronostic fonctionnel et, on l'espère, vital des patients, tout en évitant les complications liées à des interventions souvent longues chez des individus fragiles.

## Bibliographie de l'introduction


1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007 Sep;93(9):1137–46.

2. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation. 2009 Feb 3;119(4):515–23.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129–200.

4. Seferović PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, et al. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure. 2019;21(5):553–76.

5. Authors/Task Force Members, McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2012 Jul 2;33(14):1787–847.

6. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008 Oct;29(19):2388–442.

7. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart J. 2014 Oct 21;35(40):2797–815.

8. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. Circ Res. 2014 Jun 20;115(1):79–96.

9. Jeong E-M, Dudley SC. Diastolic dysfunction. Circ J. 2015;79(3):470–7.

10. Cesari M, Letizia C, Angeli P, Sciomer S, Rosi S, Rossi GP. Cardiac Remodeling in Patients With Primary and Secondary Aldosteronism: A Tissue Doppler Study. Circ Cardiovasc Imaging. 2016 Jun;9(6).

11. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. Journal of the American College of Cardiology. 2003 Oct 1;42(7):1226–33.

12. Macdonald M, Fang J, Pittman SD, White DP, Malhotra A. The Current Prevalence of Sleep Disordered Breathing in Congestive Heart Failure Patients Treated with Beta-

Blockers. Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2008 Feb 15;4(1):38.

13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017 08;70(6):776–803.

14. Quan SF, Gersh BJ, National Center on Sleep Disorders Research, National Heart, Lung, and Blood Institute. Cardiovascular consequences of sleep-disordered breathing: past, present and future: report of a workshop from the National Center on Sleep Disorders Research and the National Heart, Lung, and Blood Institute. Circulation. 2004 Mar 2;109(8):951–7.

15. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 2012 Jul 15;186(2):190–4.

16. Gonzaga CC, Gaddam KK, Ahmed MI, Pimenta E, Thomas SJ, Harding SM, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. J Clin Sleep Med. 2010 Aug 15;6(4):363–8.

17. Sim JJ, Yan EH, Liu ILA, Rasgon SA, Kalantar-Zadeh K, Calhoun DA, et al. Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population. J Hypertens. 2011 Aug;29(8):1553–9.

18. Barceló A, Piérola J, Esquinas C, de la Peña M, Arqué M, Alonso-Fernández A, et al. Relationship between aldosterone and the metabolic syndrome in patients with obstructive sleep apnea hypopnea syndrome: effect of continuous positive airway pressure treatment. PLoS ONE. 2014;9(1):e84362.

19. Giordanella JP. Rapport sur le thème du sommeil [Internet]. Ministère de la santé et des solidarités, Paris; 2006. Available from: http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/064000899.pdf

20. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002 May 1;165(9):1217–39.

21. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999 Aug 1;22(5):667–89.

22. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho M-P, Erdmann E, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015 Sep 17;373(12):1095–105.

23. Smit MD, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL, et al. The importance of whether atrial fibrillation or heart failure develops first. Eur J Heart Fail. 2012 Sep;14(9):1030–40.

24. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J. 2005 Jul 1;26(13):1303–8.

25. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. Circulation. 2016 Feb 2;133(5):484–92.

26. Samson R, Jaiswal A, Ennezat PV, Cassidy M, Le Jemtel TH. Clinical Phenotypes in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2016 Jan 25;5(1).

27. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015 Mar;8(2):295–303.

28. Gibson DG, Chamberlain DA, Coltart DJ, Mercer J. Effect of changes in ventricular activation on cardiac haemodynamics in man. Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles. Br Heart J. 1971 May;33(3):397–400.

29. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med. 2002 Jun 13;346(24):1854–62.

30. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002 Nov;23(22):1780–7.

31. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013 Apr 25;368(17):1585–93.

32. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001 Nov 15;345(20):1473–82.

33. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J. 2000 Dec;21(24):2071–8.

34. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996 Dec 26;335(26):1933–40.

35. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002 Mar 21;346(12):877–83.

36. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NAM, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004 May 20;350(21):2151–8.

37. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005 Jan 20;352(3):225–37.

38. Goldenberg I, Gillespie J, Moss AJ, Hall WJ, Klein H, McNitt S, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation. 2010 Sep 28;122(13):1265–71.

39. Smith T, Jordaens L, Theuns DAMJ, van Dessel PF, Wilde AA, Hunink MGM. The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischaemic or non-ischaemic heart disease: a European analysis. Eur Heart J. 2013 Jan;34(3):211–9.

40. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, et al. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol. 1994 Nov;17(11 Pt 2):1974–9.

41. Yu C-M, Chau E, Sanderson JE, Fan K, Tang M-O, Fung W-H, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation. 2002 Jan 29;105(4):438–45.

42. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004 May 20;350(21):2140–50.

43. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 Apr 14;352(15):1539–49.

44. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009 Oct 1;361(14):1329–38.

45. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010 Dec 16;363(25):2385–95.

46. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008 Jun 19;358(25):2667–77.

47. Hsu L-F, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med. 2004 Dec 2;351(23):2373–83.

48. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, et al. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing Clin Electrophysiol. 2006 Sep;29(9):962–70.

49. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 2014 Feb;7(1):31–8.

50. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation. 2016 Apr 26;133(17):1637–44.

51. Heeger C-H, Abdin A, Mathew S, Reissmann B, Yalin K, Liosis S, et al. Efficacy and Safety of Cryoballoon Ablation in Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction - A Multicenter Study. Circ J. 2019 Jul 25;83(8):1653–9.

52. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med. 2018 01;378(5):417–27.

53. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005 Feb;26(3):215–25.

54. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJS. Diuretics for heart failure. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD003838.

55. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003 Sep 6;362(9386):777–81.

56. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. European Journal of Heart Failure. 2018;20(8):1230–9.

57. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014 Apr 10;370(15):1383–92.

58. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015 Jan 6;131(1):34–42.

59. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2011 Aug 23;58(9):935–41.

60. Hawkins NM, Grubisic M, Andrade JG, Huang F, Ding L, Gao M, et al. Long-term complications, reoperations and survival following cardioverter-defibrillator implant. Heart. 2018;104(3):237–43.

61. Wellens HJJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J. 2014 Jul 1;35(25):1642–51.

62. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA. 2004 Dec 15;292(23):2874–9.

63. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016 29;375(13):1221–30.

64. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices

and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 May 26;

65. Malhotra S, Jr JMC. Life-Threatening Ventricular Arrhythmias: Current Role of Imaging in Diagnosis and Risk Assessment. J Nucl Cardiol. 2016 Jan 15;1–13.

66. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006 Mar 21;113(11):1424–33.

67. Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. J Am Coll Cardiol. 2012 Jun 5;59(23):2075–9.

68. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010 May 18;55(20):2212–21.

69. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013 Oct 10;369(15):1395–405.

70. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. Clin Res Cardiol. 2016 Nov;105(11):944–52.

71. De Peretti C, Pérel C, Tuppin P, Iliou M-C, Juillière Y, Gabet A, et al. Prevalence and functional status of coronary heart diseases and heart failure in the adult population in France: contribution of the “Disabilities and Health” cross-sectional surveys. Bull Epidémiol Hebd. 2014;(9–10):172–81.

72. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. Baseline characteristics of patients recruited into the CARE-HF study. Eur J Heart Fail. 2005 Mar 2;7(2):205–14.

73. Foley PWX, Chalil S, Khadjooi K, Smith REA, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronization therapy in octogenarians: a comparative study with a younger population. Europace. 2008 Nov;10(11):1302–7.

74. Rickard J, Cheng A, Spragg D, Green A, Leff B, Tang W, et al. Survival in octogenarians undergoing cardiac resynchronization therapy compared to the general population. Pacing Clin Electrophysiol. 2014 Jun;37(6):740–4.

75. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J, et al. Response to cardiac resynchronization therapy in elderly patients (≥70 years) and octogenarians. Eur J Heart Fail. 2013 Feb;15(2):203–10.

76. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 02;321(13):1261–74.

77. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 02;321(13):1275–85.

78. Dagres N, Bongiorni MG, Larsen TB, Hernandez-Madrid A, Pison L, Blomström-Lundqvist C, et al. Current ablation techniques for persistent atrial fibrillation: results of the European Heart Rhythm Association Survey. Europace. 2015 Oct;17(10):1596–600.

79. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. Circ Arrhythm Electrophysiol. 2015 Feb;8(1):18–24.

80. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H, et al. EHRA White Paper: knowledge gaps in arrhythmia management-status 2019. Europace. 2019 Mar 18;

81. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque J-P, Kautzner J, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. Circulation. 2015 Sep 8;132(10):907–15.

82. Sporton SC, Earley MJ, Nathan AW, Schilling RJ. Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. J Cardiovasc Electrophysiol. 2004 Mar;15(3):310–5.

83. Estner HL, Deisenhofer I, Luik A, Ndrepepa G, von Bary C, Zrenner B, et al. Electrical isolation of pulmonary veins in patients with atrial fibrillation: reduction of fluoroscopy exposure and procedure duration by the use of a non-fluoroscopic navigation system (NavX). Europace. 2006 Aug;8(8):583–7.

84. Bertaglia E, Bella PD, Tondo C, Proclemer A, Bottoni N, De Ponti R, et al. Image integration increases efficacy of paroxysmal atrial fibrillation catheter ablation: results from the CartoMerge Italian Registry. Europace. 2009 Aug;11(8):1004–10.

85. Della Bella P, Fassini G, Cireddu M, Riva S, Carbucicchio C, Giraldi F, et al. Image integration-guided catheter ablation of atrial fibrillation: a prospective randomized study. J Cardiovasc Electrophysiol. 2009 Mar;20(3):258–65.

## PROBLEMATIQUE

Nous avons décrit dans l'introduction l'importance de la prise en charge rythmologique des patients en situation d'IC, qu'il s'agisse d'améliorer les symptômes, éviter les facteurs aggravants et réduire la mortalité. Cependant, certaines limites persistent et à partir des quatre thèmes précédemment développés, nous avons élaboré quatre projets de recherche pour constituer ce travail.

1. L'évaluation d'un algorithme de détection du SAS au sein du stimulateur cardiaque chez des patients présentant une altération de la fonction diastolique.
2. L'évaluation de l'intérêt d'utiliser l'IRM pour la mesure de la FEVG, comparée à l'échographie cardiaque bidimensionnelle, pour la prédiction des évènements cardiaques chez des patients implantés d'un DAI prophylactique.
3. L'évaluation de la réponse à la RC et ses facteurs prédictifs chez les patients de 75 ans et plus.
4. L'évaluation de la sécurité d'utilisation et de l'efficacité d'un système de CEA ultra-haute densité dans l'ablation des troubles du rythme supra-ventriculaires complexes chez des patients en IC.

# 1ère partie : Les algorithmes de détection du SAS présents dans les stimulateurs cardiaques peuvent-ils améliorer la prise en charge des patients appareillés porteurs d'une dysfonction diastolique ? L'étude SAPAAD.

Le SAS a une prévalence très importante chez les patients porteurs de PM et certains dispositifs proposent des algorithmes de détection automatisée.

Nous avons mis au point une étude prospective non randomisée dont l'objectif principal était de valider la détection du SAS sévère par un de ces algorithmes, le SAM (Sleep Apnea Monitoring, Microport Sorin™, Clamart, France), chez des patients appareillés et porteurs d'une DD. L'index du SAM, le Respiratory Disturbance Index (RDI) et sa valeur moyenne sur 30 jours (RDIm) ont été comparés à l'index apnées hypopnées (IAH) obtenu au cours d'une polygraphie ventilatoire (PV) nocturne à deux mois.

Les objectifs secondaires étaient : le suivi des patients traités par PPC, la performance diagnostique de l'algorithme dans la détection du SAS modéré à sévère, la corrélation entre le SAS et les niveaux d'aldostérone plasmatique au diagnostic et sous PPC, les caractéristiques du SAS dans cette population de patients souffrant de DD, la survenue d'arythmies.

Nous avons inclus 68 patients entre juin 2016 et décembre 2018, une majorité d'hommes (60%), âgés de 80±8 ans, et dont le BMI moyen était 26,6±4,6 kg/m². La DD a pu être quantifiée chez 61 patients, ceux qui étaient en rythme sinusal au moment de l'échocardiographie : la majorité d'entre eux (61,8%) avaient une DD de grade 1, 23,5% de grade 2, et 4,4% de grade 3. Parmi les patients inclus, 63 ont réalisé la PV et ont été inclus dans l'analyse des objectifs de l'étude. La prévalence totale du SAS était de 83,8%. Un SAS sévère a été diagnostiqué chez 23,5% des patients par la PV. La corrélation entre les index

était bonne avec un coefficient de corrélation intra-classe de 0,76 (IC 95% 0,60 à 0,86, p<0,001) entre le RDI et l'IAH, et de 0,61 (IC 95% 0,35 à 0,76, p<0,001) entre le RDIm et l'IAH. Les valeurs optimales de RDI et RDIm pour le diagnostic de SAS sévère, déterminées par la méthode de ROC était respectivement de 22/heure (aire sous la courbe 0,75±0,08 ; IC 95% 0,59 à 0,91, p=0,007) et 19/heure (aire sous la courbe 0,73±0,09, IC 95% 0,56 à 0,91, p=0,011). Les critères de performance diagnostique du RDI et RDIm étaient : sensibilité de 71,4% et 60%, et spécificité de 65,2% et 66% respectivement.

Sous PPC, le RDI (p=0,041) et le RDIm (p=0,039) diminuaient de façon significative, tout comme l'IAH (p=0,002). L'aldostérone plasmatique était significativement plus basse après deux mois de traitement par PPC (231±157 versus 167±111 pmol/l, p=0,034), mais n'était pas corrélée à la sévérité du SAS ni à celle de la DD. Nous avons observé que les patients ayant un SAS sévère avaient tendance à avoir une onde E mitrale (p=0,079), ainsi qu'un rapport E/e' latéral (p=0,122) plus élevés, sans que la présence d'un SAS sévère ne soit corrélée de façon significative aux grades de sévérité de la DD. Enfin, nous avons mis en évidence des taux élevés d'épisodes d'arythmies supraventriculaires chez tous patients, mais sans différence significative entre les patients présentant un SAS sévère et les autres.

Nous avons donc pu montrer que l'algorithme SAM permettait de façon fiable de dépister le SAS dans une population de porteurs de PM et ayant une DD, mais aussi de suivre son évolution sous traitement. Ces patients sont à haut risque d'évoluer vers une IC-FEp, notamment en cas d'apparition d'un SAS et/ou de FA, il est donc important de pouvoir s'aider des informations fournies par le PM pour dépister précocement ces pathologies associées et les traiter si besoin.

**Articles**

1) Revue de la littérature et méthodologie de l'étude :

   **Champ-Rigot L**, Ferchaud V, Prévost JN, Moirot P, Pellissier A, Legallois D, Alexandre J, Scanu P, Morello R, Saloux E, Milliez PU.

   *Rationale and Design for a Monocentric Prospective Study: Sleep Apnea Diagnosis Using a Novel Pacemaker Algorithm and Link With Aldosterone Plasma Level in Patients Presenting With Diastolic Dysfunction (SAPAAD Study).*

   Clin Med Insights Cardiol. 2018 Jan 8;12:1179546817751628. doi: 10.1177/1179546817751628. eCollection 2018.

2) Résultats de l'étude: Usefulness of sleep apnea monitoring by pacemaker sensor in elderly patients with diastolic dysfunction: the SAPAAD Study

**Rationale and design for a monocentric prospective study: Sleep Apnea diagnosis using a novel Pacemaker Algorithm and link with Aldosterone plasma level in patients presenting with Diastolic dysfunction (SAPAAD Study)**

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## ABSTRACT

Previous studies showed good agreement between pacemaker respiratory disturbance index (RDI) and polysomnography for diagnosis of severe sleep apnea (SA). The aim of this study is to investigate the diagnostic accuracy of RDI compared to apnea hypopnea index (AHI) from a cardiorespiratory sleep study for the diagnosis of severe SA within patients requiring a pacemaker and meeting diastolic dysfunction criteria. Secondary objectives are: correlation between plasma aldosterone level and SA severity, diagnostic accuracy of RDI for moderate SA; prevalence of SA among patients with diastolic dysfunction; occurrence of arrhythmias; improvement of RDI with continuous positive airway pressure therapy. We designed a monocentric prospective non-randomized study of prevalent cases to include 68 patients with a six-month follow-up. RDI and AHI will be compared two months after implantation and after one month of continuous positive airway pressure treatment in patients with severe SA. This is the first study that examines diagnostic accuracy of pacemaker algorithm for the diagnosis of SA and correlation with plasma aldosterone levels in patients with diastolic dysfunction.

**KEY WORDS:** Sleep apnea, Diagnosis, Attended cardiorespiratory sleep study, Diastolic dysfunction, Aldosterone

# INTRODUCTION

## Sleep apnea, impaired diastolic function and hyperaldosteronism

Sleep apnea (SA) affects 5 to 7% of the general population and reaches 15% of people over 70 years[1,2]. Its prevalence is very high among patients with hypertension or other cardiovascular diseases such as coronary artery disease, heart failure (HF), stroke or atrial fibrillation (AF)[3]. It has been shown that SA is a risk factor for these conditions. Underlying mechanism is mostly obstructive resulting in collapse of the upper airways at pharyngeal level during sleep. Conversely central SA is less frequent and often associated with HF[4,5]. SA has a particularly high prevalence among patients who have indication for cardiac pacing reaching 60%[6]. It has also been associated with ventricular arrhythmias and nocturnal sudden cardiac death[7]. Sleep related breathing disorders result in nocturnal intermittent hypoxemia. This lead to chronic reflex activation of the sympathetic nervous system, vascular vasoconstriction, production of vasoactive substances such as endothelin, oxidative stress and finally endothelial dysfunction[4].

HF with preserved left ventricular ejection fraction (LVEF) accounts for almost 50 % of HF cases. It is defined by clinical signs of HF, with a normal LVEF associated with other features like abnormal relaxation, filling or diastolic stiffness[8]. Diastolic dysfunction appears as the first stage of this particular type of HF but can also be found in patients with no clinical sign of HF. Relaxation abnormalities increase with age, diabetes, hypertension, cardiomyopathy, impaired systolic function[9]. Until now there is no published data about the prevalence of obstructive SA in this specific subgroup of patients presenting a diastolic dysfunction. On the other hand SA has been recognized as an independent risk factor for hypertension[10] and several studies have shown a very high prevalence of obstructive SA in patients with resistant hypertension and associated hyperaldosteronism[11].

## Sleep apnea diagnosis

Obstructive SA is often under diagnosed by clinical examination due to numerous and non specific symptoms. Moreover, better related symptoms like snoring, apneas and excessive day-time sleepiness are often lacking in patients with cardiovascular disorders. Confirmation tests are expensive and their access is limited with significant waiting lists. The gold standard remains the polysomnography (PSG) but type 3 portable monitors exhibit good diagnostic performance[12]. The recording is performed at home or during attended cardiorespiratory sleep study (ACSS). Apnea hypopnea index (AHI) represents the sum of apnea and hypopnea episodes per hour of sleep. It's considered abnormal if greater than or equal to five per hour.

## Sleep apnea diagnosis with pacemakers

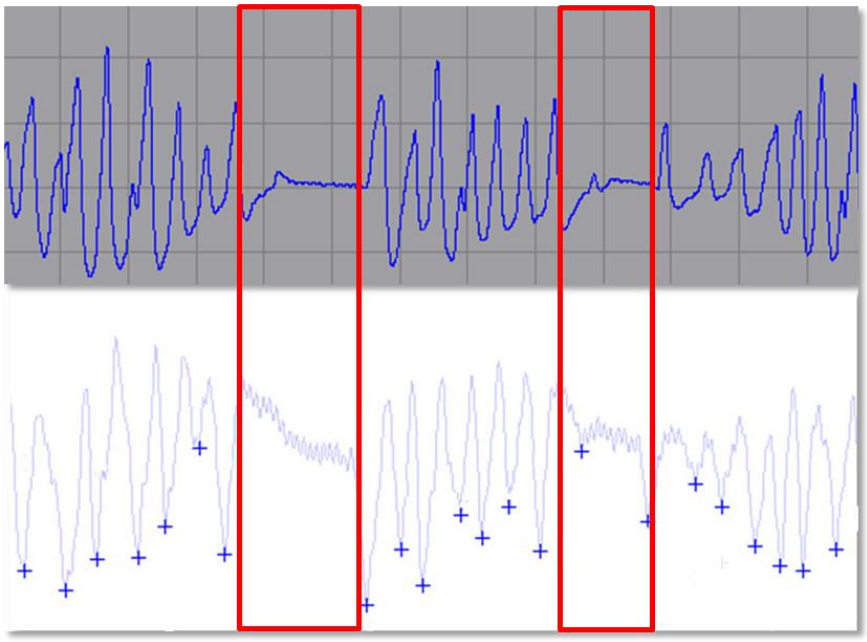
The Sleep Apnea Monitoring (SAM) algorithm uses a rate-responsive pacemaker (PM) sensor, providing an index of minute ventilation derived from measurements of real-time transthoracic impedance variation[13]. SAM thus detects two types of events: apneas (absence of significant respiratory cycle for more than 10 seconds) and severe hypopneas (50% or more decrease in minute ventilation compared to the mean value over the last breathing period sustained for more than 10 seconds) as shown in Figure 1. These events are then reported with the respiratory disturbance index (RDI) which is the average number of events (apnea or hypopnea) detected per hour of estimated sleep (see Figure, additional file 1, which illustrates SAM data available during PM interrogation). The new version of the SAM algorithm was developed with better management of noise.

We performed a review of published studies in English on Pubmed database using the following key words: "sleep apnea" and "pacemaker". This research provided 87 citations. After exclusion of those that didn't assess diagnostic accuracy of PM, seven citations remained. Major findings are summarized in Table 1. Two were performed with PM that didn't allow automatic treatment of the transthoracic impedance[15,16] and the signal was processed and

analyzed using a dedicated software. All studies[13–18] except one[19] used PSG as reference test but with different AHI threshold values according to SA severity required for diagnosis. Designs were different and therefore diagnostic accuracy statistics are difficult to compare.

**Figure 1: Nasal flow measured during polysomnography (top window) and corresponding recording of transthoracic impedance signal by the minute ventilation sensor (bottom window).**

Two apneas are recorded with the fall of the nasal pressure for more than 90% and the concurrent decreasing of the transthoracic impedance signal from the pacemaker. Reprinted with permission from Defaye et al[14].



Padeletti et al didn't report if patients were correctly classified for SA based on PM index but only correlation between mean values of AHI from PM and in-home respiratory monitoring[19]. In Aimé et al study only apneic patients based on PM index (40/61 patients, 65.6%), were proposed to undergo PSG[17]. Only 65% of them realized the reference test and the positive predictive value of PM index could be overestimated. Despite these discrepancies, these studies exhibit a good agreement between the PM derived RDI and AHI from PSG[13–16]. Correlation coefficient between the two tests was found to be similar to other home-based PSG

recording systems[15,18]. Nevertheless, it was shown that systematic bias between the two methods was higher in patients with severe SA[14,15,18]. The recently published report from Dias et al. also shown that in spite of good correlation between RDI and AHI values, the agreement between SAM algorithm and PSG was poor regarding SA diagnosis and severity assessment (kappa coefficient=0.167)[18]. All studies showed good diagnostic accuracy of PM indexes. Defaye et al. reported in the most recent prospective multicenter study a sensibility (Se) of 88.9% and a specificity (Sp) of 84.6% compared to PSG for the diagnosis of severe SA (AHI≥30/h). The best threshold value of RDI to predict patients with severe SA was 20 events / hour[14]. The same team found a different cut-off with a previous version of the algorithm[13]. Likewise, the cut-off value was also different when using another type of PM without automatic signal processing[16]. Aimé et al work is also interesting as they investigated diagnostic accuracy of both short term RDI from last 24 hours and the “smoothed” index calculated by averaging the overall number of apneas and hypopneas over the period between two follow-up visits. There was a good correlation between these indexes and moreover the smoothed index had a better sensitivity to detect SA than the short term index[17]. Among these studies, only one reported data about arrhythmias. The incidence of AF or other rhythm disorders was similar in patients with and without SA, based on in-home respiratory monitoring (AHI≥10/h)[19].

**Aim of the study**

The present study investigates the diagnostic performance of the RDI given by the PM compared to the result of ACSS realized in the sleep laboratory for the diagnosis of severe SA and the correlation with plasma aldosterone levels in a population of patients presenting with diastolic dysfunction.

**Table 1: Review of published studies comparing PM algorithm and sleep studies for SA diagnosis**.

Data note available were calculated if possible, otherwise non available (NA). Values are mean±standard deviation. In Dias et al 60 patients were recruited but 6 excluded for non-available RDI; age and BMI are the median and interquartile range. M: male; F: female; BMI: body mass index; TTI: trans-thoracic impedance; AHI: apnea-hyponea index (events per hour); ROC: receiver operating curve; RDI: respiratory disturbance index(events per hour); PSG: polysomnography; Se: sensibility; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; 95%CI: confidence interval at 95 percent; MD: mean difference or systematic bias(event per hour); 2SD: 2 standard deviations or limit of agreement.

| Author | N patients (M/F) | Age (years) | BMI (kg/m²) | Device | TTI signal analysis | Reference test (AHI threshold) | Prognostic value | ROC curve (AUC, cut-off value) | Agreement (Bland and Altman/ Pearson correlation coefficient r) |
|---|---|---|---|---|---|---|---|---|---|
| **Defaye et al 2004[13]** | 42 (30/12) | 70±8 | 26±4 | Talent 3™ (ELA Medical) | Automatic RDI during estimated sleep | PSG AHI≥30/h | Se=75% Sp=94% PPV=75% NPV=94% | AUC=0.75 (95%CI: 0.6-0.87) for AHI≥30 Cut-off = 30.6 | MD=0.9 (95%CI: -3.6-5.4) p>0.2 2SD =30 Pearson's r NA |
| **Scharf et al 2004[14]** | 22 (14/8) | 65.6±13.4 | 28±5.8 | Kappa™ 400 (Medtronic) | No automatic signal treatment Manual scoring by investigators | PSG AHI >20/h | Se=100% Sp=100% | AUC=1.0 for AHI≥20 AUC=0.966±0.37 for AHI≥15<br>AUC=0.95±0.05 for AHI≥5 | MD=-1.5±10.6 p<0.05 2SD=20.8<br>Pearson's r=0.869 p<0.001 |
| **Shalaby et al 2006[15]** | 60 (45/15) | 69±12 | 30±6 | Pulsar Max™ Pulsar Max II™ Insignia Plus ™ (Guidant) | No automatic signal treatment Automatic algorithm developed by the investigators | PSG AHI ≥30/h | Se=82% Sp=88% | AUC= 0.91 for AHI≥30 Cut-off= 39<br>AUC=0.85 for IAH≥15 Cut-off=37 | MD= 2.5 2SD=34.2<br>Pearson's r=0.8 p<0.01 |
| **Padeletti et al 2010[18]** | 20 (15/5) | 78 | 25.5 | Talent 3™ DR (ELA Medical) | Automatic RDI during estimated sleep | In-home respiratory monitoring AHI>10/h | NA | NA | Pearson's r: NA AHI=27±14 PM RDI=16±13 p = 0.15 |
| **Defaye et al 2014[16]** | 40 (27/13) | 73.8±19 | 27.7±4.4 | REPLY 200™ SR / DR (Sorin CRM) | Automatic RDI during estimated sleep | PSG AHI≥30/h | Se=88.9% Sp=84.6% PPV=88.9% NPV=84.6% | AUC= 0.91 (95%CI: 0.8-1.0; p<0.001) for AHI≥30 cut-off=20 | MD=9.2±11.6 2SD= (-14 to 32.4) p value NA Pearson's r NA |
| **Aimé et al 2014[17]** | 61 (50%) | 71.4±10.9 | 26.6±4.1 | Talent 3™ DR (ELA Medical) | Automatic RDI during estimated sleep | PSG AHI≥15 | PPV=84.6% | NA | NA |
| **Dias et al 2017[18]** | 54 (31/23) | 77 (69-81) | 27 (23-30) | REPLY 200™ SR/DR (Livanova) | Automatic RDI during estimated sleep | PSG AHI≥5<br>AHI≥15 | Se= 80% Sp=79%<br>Se=100% Sp=70% | AHI≥5; cut-off=10 AUC=0.81 (95%CI: 0.68-0.95)<br>AHI≥15; cut-off=13 AUC= 0.86 (95%CI:0.76-0.95) | MD=0.7±14.7 2SD= 33.3<br>Pearson's r=0.522 (p<0.001) |

## METHODS

### Study design and ethics

The SAPAAD study is a prospective, single-center, diagnostic cohort study. The institutional review board of the University Hospital of Caen (19 November 2015) and the ethics committee (CPP Nord-Ouest III, 5 March 2016) approved the study as well as the Agence Nationale de Sécurité du Médicament (Register number: 2016-A00034-47, 4 March 2016). The SAPAAD study was registered on 25 April 2016 on the ClinicalTrials.gov website with trial identification number NCT02751021. The SAPAAD study follows the SPIRIT guidelines[20]. The flow chart of the protocol is shown in Figure 2. All patients provided written informed consent prior to their enrollment for the study participation, use and disclosure of their information in publications.

### Study population

Consecutive patients with clinical and electrical indication for permanent cardiac pacing, scheduled or not, will be screened. According to current European Guidelines[21] patients are presenting either with third degree atrioventricular block, second degree atrioventricular block mobitz 2 type, bundle branch block associated with syncope and infra-hisian block at electrophysiological study, symptomatic sinus node dysfunction including brady-tachy form of sick sinus syndrome or bradyarrhythmia. Patients with diastolic dysfunction diagnosed at the transthoracic echocardiography (TTE) are eligible for the study. Patients fulfilling one of these criteria will not be included: younger than 18 years old, lack of informed consent form, impossibility to fit in the scheduled study plan, indication for cardiac resynchronization or LVEF lower than 45%, indication for epicardial PM, known severe SA treated by continuous positive airway pressure (CPAP).

**Standard procedures**

- *Transthoracic echocardiography*

According to our standard of care, all patients undergo a TTE before a PM implantation. This exam is conducted at the Echocardiography laboratory in Caen University Hospital, using Epic 7® (Philips Healthcare), during left lateral decubitus, with simultaneous electrocardiogram (ECG) monitoring.

- *PM implantation*

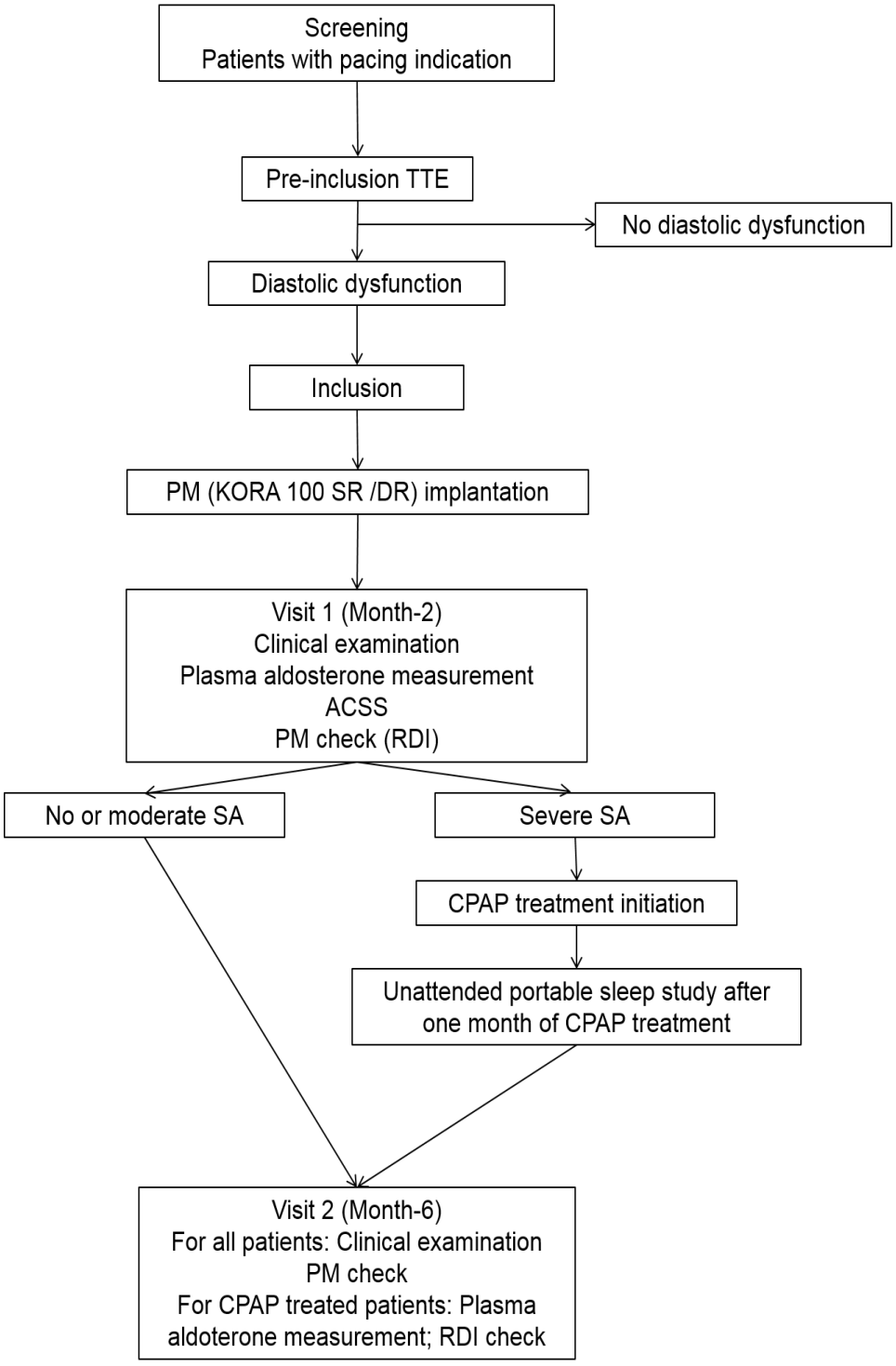
Implantation is realized at the Heart Rhythm Unit of Caen University Hospital according to current guidelines and local standard of care. The procedure is performed under local anesthesia and implantation is preferentially carried out in left pre pectoral subcutaneous pocket, with puncture of the left cephalic vein or if necessary the left subclavian vein, then positioning the right ventricular lead apical or septal, and an atrial lead in the right appendage or on the side wall of the right atrium if required. Choice of the leads is at the discretion of the operator, and the device is a KORA 100 single or double room (LivaNova). On the second day after implantation, we perform clinical exam (in particular the wound), ECG with and without magnet, device checking and programming and a chest X-ray. Patient is discharged if there is no complication.

- *PM follow-up*

Two months after hospital discharge, all patients undergo a follow-up visit with clinical examination and device control. Impedance, sensibility and stimulation thresholds are measured and PM memories are read. Arrhythmias, mean heart rate, stimulation rate and RDI are collected. The next follow-up is scheduled six months after implantation. If appropriate, data are collected for the first month of CPAP treatment.

**Figure 2: Study flow chart**

TTE: transthoracic echocardiography; PM: pacemaker; SR: single room; DR: double room; ACSS: attended cardiorespiratory sleep study; RDI: respiratory disturbance index; SA: sleep apnea; CPAP: continuous positive airway pressure



**Interventions**

- *Clinical examination*

Special concerns are taken during clinical examination in order to detect physical signs or symptoms that might be related to SA. Weight, height and body mass index are systematically reported. Patients are asked about daytime sleepiness, drowsiness, snoring and other symptoms less frequent like nocturia, nocturnal chocking or gasping. We use the Epworth clinical scale (see table, additional file 2, which reports items and scoring of the scale) and the Berlin questionnaire (see table, additional file 3, which reports items and scoring of the questionnaire) in order to estimate a pre-test probability of SA.

- *Attended cardiorespiratory sleep study (ACSS)*

The ACSS is conducted in the sleep laboratory of Caen University Hospital. Monitoring is performed by usual methods of the center with a type 3 portable monitor (CID 102L, Cidelec, France). Recorded signals are: nasal flow, pulse oxymetry, respiratory inductance plethymosgraphy, brightness, supra sternal pressure, body position, actimetry and analysis of respiratory sounds. The recording will be analyzed using Cidelec software by a practitioner with a board certification in sleep medicine in order to characterize nocturnal events and calculate the AHI of the study night. Mild SA is defined by an AHI between five and 15 events per hour, moderate SA by an AHI between 15 and 30 per hour and severe SA if AHI is greater than or equal to 30 events per hour.

A self-questionnaire is given to the patient about the quality of sleep during the night recorded (estimated latency of sleep and awakening, number of nocturnal arousals and pattern, presence of dream activity, restful sleep or not). A blood punction is realized previous to the ACSS for blood gas measures. This sample will also be used for aldosterone test.

- *Plasma aldosterone level measurement*

Blood samples are centrifugated within 30 minutes, and 1-mL plasma aliquots are immediately frozen and stored at −80°Celsius. Plasma aldosterone concentrations are measured with a commercially available radioimmunoassay kit (Beckman Coulter Immunotech, France).

- *SA treatment*

A specific treatment with nocturnal CPAP ventilation is proposed to all patients with a severe obstructive SA diagnosed (AHI≥30/h). If central mechanism is mainly responsible for SA, the type of ventilation can be different for example adaptative servo-ventilation. CPAP device and settings are decided by the sleep physician according to patients' profile. Device is provided by the AIR de Basse-Normandie association. One month after the beginning of CPAP therapy, patients will have a control unattended sleep study with a portable monitor. Compliance to ventilation is evaluated from nightly duration of CPAP use. Effectiveness is assessed using clinical evaluation of sleepiness and the decrease of AHI.

**Study endpoints**

The primary objective is the diagnostic accuracy of RDI compared to AHI for the diagnosis of severe SA. Secondary objectives are: correlation between plasma aldosterone level, sleep apnea severity and its improvement with specific treatment; diagnostic accuracy of RDI compared to AHI for the diagnosis of moderate sleep apnea; prevalence of sleep apnea among patients with diastolic dysfunction; occurrence of atrial and ventricular arrhythmias; improvement of RDI with CPAP. Judgment criteria for all the objectives are listed in Table 2.

**Table 2: Study endpoint measures**

PM : pacemaker ; CPAP : continuous positive airway pressure ; AHI : apnea hypopnea index ; RDI : respiratory disturbance index ; ACSS: attended cardiorespiratory sleep study; SA : sleep apnea; AF: atrial fibrillation

| | Endpoint | Judgment criteria |
|---|---|---|
| **Primary endpoint measure** | Diagnostic accuracy of RDI compared to AHI for the diagnosis of severe sleep apnea (AHI greater than 30 events per hour) | Comparison between RDI (value of the sleep study recording night and mean RDI of the previous month) and AHI from the ACCS for the diagnosis of severe SA |
| **Secondary endpoint measures** | Correlation between plasma aldosterone levels, sleep apnea severity and its evolution with specific treatment | Measurement of plasma aldosterone two months after PM implantation and one month after CPAP in apneic patients and correlation with AHI |
| | Diagnostic accuracy of RDI compared to AHI for the diagnosis of moderate sleep apnea (AHI between 15 and 30 events per hour) | Comparison between RDI (value of the sleep study recording night and mean RDI of the previous month) and AHI from the ACSS for the diagnosis of moderate SA |
| | Prevalence study of sleep apnea among patients with diastolic dysfunction | Number of patients with mild SA (AHI between 5 and 15 events per hour), moderate (AHI between 15 and 30 events per hour) and severe (AHI greater than 30 events per hour), number of subjects with obstructive or central SA based on the ACSS results |
| | Occurrence of atrial and ventricular arrhythmias | AF burden, mean duration of AF episodes, percentage of atrial and ventricular stimulation, episodes of ventricular arrhythmias |
| | Improvement of RDI with CPAP | Comparison between RDI and AHI after CPAP for patients with severe SA |

**Sample size estimation**

Data from the literature on the diagnostic performance of type 3 portable monitors compared with the PSG show variable results with a sensitivity between 61 and 91%[22,23]. To highlight an agreement (measured by the intraclass correlation coefficient) between the RDI and AHI of at least 0.80, for an alpha risk equal to 5% and 90% power, 63 patients must be recruited[24]. We plan therefore to recruit 68 patients, considering that there is a risk that for about 5% of patients to have data not fully exploitable (lost sight of missing data, etc.).

**Statistical plan**

The continuous quantitative variables are expressed by mean and standard deviation and qualitative variables are the number of patients and percentages. The occurrence and severity of SA are evaluated only in patients who have undergone ACSS. The diagnostic performance of the SAM algorithm for screening moderate (15≤AHI≤30 events per hour) and severe SA (AHI≥30 events per hour) is evaluated by calculating the area under the Receiver Operator Characteristic Curve, with (1-Sp) on x-axis and Se on the y-axis. The best threshold value of RDI to discriminate populations (patients without moderate SA and patients with moderate to severe SA, patients without severe SA and patients with severe SA) is the one that gives the best compromise between Se and Sp, corresponding to the area under the curve nearest from 1. 95% confidence intervals for both Se and Sp, positive and negative predictive values as well as positive and negative likelihood ratios of the RDI are calculated. The agreement between RDI and AHI for the detection of moderate and severe SAS is evaluated firstly by the Bland and Altman method and also by the intraclass correlation coefficient. The significance level used is $p < 0.05$. Statistical analyzes are performed with IBM-SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).. Data are analyzed in intention to treat.

**Feasibility**

We implant in our center almost 300 single and dual chambers PM each year. The prevalence of diastolic dysfunction (stage I to III) is about 45% in patients over 65 years and reaches almost 70% in patients over 75 years[9]. Taking into account patients exclusions either for refusal or if already under CPAP, we can assume recruiting all patients required in the study within 18 months.

**Registration**

The data will be collected and registered using electronic case report forms (e-CRF) by a dedicated local technical research team using the OpenClinica open source software, version 3.13 (Copyright © OpenClinica LLC and collaborators, Waltham, MA, USA, www.OpenClinica.com).

**Data collected**

Baseline characteristics will be collected: age, sex, weight, height, body mass index, smoking status, caffeine and alcohol consumption, history and type of diabetes mellitus, history of cardiovascular disease (hypertension, coronary artery disease, valvular heart disease, arrhythmias, cardiac medications), pacemaker indication, heart rhythm (sinus or AF), heart rate, Berlin questionnaire result and Epworth score. During follow-up visits (month-2, month-6), clinical variables, Epworth and Berlin scores will be recorded.

During screening TTE the following will be recorded: in 2-dimension mode: systolic and diastolic diameter of the left ventricle, interventricular septal wall thickness, left atrium (LA) diameter and volume, LVEF with Simpson method, left ventricular outflow track diameter; in pulse-wave mode: left ventricular outflow track diameter flow, left ventricle filling with E and A waves velocity, A wave duration, E/A ratio; study of pulmonary vein flow with S/D waves ratio and A reverse wave duration; in continuous–wave mode: trans aortic flow, aortic valve area;

in color M mode: slope of left ventricle filling flow; in TDI mode: Ea wave at lateral and septal mitral annulus, E/Ea ratio at lateral and septal mitral annulus.

Data from PM implantation will be recorded: type of PM (single or double room), implantation site (left or right and pre or retropectoral), position of the atrial and ventricular leads, intraoperative complications (tamponade, pneumothorax, excessive blood loss, life-threatening arrhythmias) and device programming.

During ACSS different data will be collected: duration of recording, mean and lowest oxygpulse oxymetry, duration with oximetry below 90 % and below 85%, snoring index, and the AHI.

Blood samples will be taken during month-2 follow-up visit and at month-6 follow-up visit in case of CPAP treatment (arterial blood gas and plasma aldosterone).

Data monitoring will be performed by Clinical Research Unit of the Caen University Hospital.

**Adverse events**

Security of patients will be routinely assessed according to the center's standard of care and current guidelines. Serious adverse events will be reported in a dedicated form in the e-CRF and immediately declared to authorities by study promoter. Expected adverse events, related to associate drugs, disease progression or standard procedures listed in the study protocol will be reported in the e-CRF and declared at the end of the study in the security final report.

**Study organization**

The study promotion is performed by the University Hospital of Caen, France. The study is funded thanks to financial support from both the University Hospital of Caen and Sorin LivaNova (Sorin Group France SAS, Clamart).

**Duration and timeline**

Patients from the University Hospital of Caen will be included during 18 months. The protocol, approval from the ethical committee, financial support and electronic case report forms were developed in 2015 and 2016. Inclusion and follow-up of patients are planned until first semester of 2018. The database will be closed in 2018, after which data analysis, manuscript writing, and submission for publication will follow.

## DISCUSSION

SA is frequent especially in patients with heart disease and is underdiagnosed due to poor clinical presentation. Obstructive SA is associated with a poor quality of life and represents a major health problem, acting as an independent risk factor for cardiovascular morbidity and mortality[25]. CPAP can improve both respiratory parameters and prognosis of related comorbidities[26,27].

Diastolic dysfunction is a common finding in the elderly, especially in case of diabetes or hypertension and represents a first step towards HF with preserved LVEF. All-cause mortality in a cohort study from general population was higher among participants who had diastolic dysfunction after adjustment for age, sex, and LVEF[9]. Despite some conflicting data, it now seems fairly clear that patients with moderate to severe SA have a high prevalence of relaxation abnormalities. The severity of obstructive SA expressed by AHI is correlated with the early diastolic velocity (Ea) by Tissular Doppler Imaging (TDI) after adjustment for other known variables[28]. Furthermore, the effective treatment of obstructive SA with CPAP ventilation prevents the worsening of diastolic function echocardiographic parameters and even reverses them in early stages[29,30]. On the other hand, little is known about SA prevalence among patients presenting with diastolic dysfunction although it is a frequent finding among PM recipients and is probably correlated to high plasma aldosterone levels. It has already been observed that primary aldosteronism is associated with left ventricular remodeling and diastolic

function impairment which is reversible with adrenalectomy[31,32]. Therefore, it seems very important to improve SA detection, because SA may worsen prognosis in this specific population.

The SAM algorithm developed by LivaNova is a new screening tool for SA diagnosis. There are several data on its accuracy[13,14,17,19] and a prospective study already showed that the RDI was well-correlated with PSG[14]. The interest of our study is to validate the diagnostic accuracy of the SAM algorithm within a particular subgroup of patients. We assume that in this population this algorithm could be an effective screening tool allowing to detect suspect high risk patients for SA and to address them to a sleep specialist. In addition, if the RDI is low it would be possible to rule out SA with no need of a time-consuming, expensive test like a PSG.

Unlike Defaye et al[14], we chose attended sleep study with type 3 portable monitor as reference test. Diagnostic accuracy of ACSS is lower than complete PSG but it can be used as an alternative for the diagnosis of SA[12] especially in patients with high pretest probability of moderate to severe SA. With lower cost and easier implementation than PSG, ACSS represents a more “real life” gold standard.

The choice of the primary judgment criteria was also challenging. We want to take into account two values of RDI: the one of the sleep study night but also the mean value over the previous month. It’s probably methodologically better to compare two variables recorded at the same time. However, we know that one limiting factor of sleep studies is sleep quality and reproducibility of AHI measured on a single night resulting in false-negative results. Since the algorithm provides RDI values over a six-month period, we assume that average RDI from previous month might be a more relevant data than a single night value. This feature may compensate the weakness of a single-signal recording by the SAM algorithm compared to ACSS result based on several signals. Aimé et al suggested already that a “smoothed” index should more sensitive to detect SA[17]. Finally, the decrease of RDI, like the AHI, after CPAP treatment will also test the agreement between these two values. The follow-up of RDI after CPAP therapy could be an alternative to a control sleep study.

Among hypertensive patients, SA prevalence is increased in patients with hyperaldosteronism[33]. Moreover the severity of obstructive SA is correlated to the level of plasma aldosterone[33–35]. Recently it has been shown that plasma aldosterone levels are significantly higher in apneic patients and that CPAP treatment reduces plasma aldosterone levels[36]. Our study is the first one to examine the relationship between SA and plasma aldosterone level in a specific population of patients presenting with diastolic dysfunction related to systemic hypertension or not. We aim to better understand the role of hyperaldosteronism in this particular situation and the beneficial effect of CPAP treatment. It could support the use of Renin-angiotensin-aldosterone system blockers in case of systemic hypertension requiring drug therapy in this particular group of patients.

SAM algorithm has been exclusively studied for diagnosis of severe SA. As a secondary objective, we aim to show the level of agreement between RDI and AHI for diagnosis of moderate SA. Even these patients don't require CPAP treatment; they have to be closely followed by a sleep specialist and they can benefit from non-CPAP treatment.

As SA is a well-known risk factor for arrhythmias, PM memories are very useful to diagnose nocturnal arrhythmias related to SA and the potential improvement with CPAP treatment. Padeletti et al didn't find any difference in arrhythmias incidence between SA an non SA patients but their patients were probably less severe than ours since their diagnostic cut-off AHI was 10 events/hour[19]. Severe obstructive SA can also influence atrioventricular conduction abnormalities and evolution of pacing rates after CPAP treatment could be relevant.

Some comments could be addressed concerning the limitations of the study. Firstly, the study population is limited to patients with diastolic dysfunction in order to observe high prevalence of obstructive SA without a control group of patients with no diastolic dysfunction. Further studies may be conducted to evaluate the diagnostic accuracy of the SAM in a population with a lower prevalence of obstructive SA. The echocardiographic analyses of diastolic dysfunction can also be challenging due to the initial bradycardia requiring PM implantation. The choice of

ACSS with type III portable monitor is also a limit of our study as it is not the gold standard for SA diagnosis. Past studies have shown a good diagnostic accuracy of this test compared to PSG in patients with high pretest probability and for the diagnosis of moderate to severe SA. Especially in patients with other types of sleep relating breathing disorders, ACSS could underestimate SA diagnosis. Considering our population with a high probability of SA we assume that ACSS could represent a reliable standard test. As we discussed earlier it is the most widespread test to confirm SA diagnosis in daily practice. We chose to evaluate the benefit of CPAP therapy at one month. Improvement of both indexes is supposed to happen as soon as CPAP is used, arrhythmias and heart rate should also decrease quickly if they were related to severe SA. However, this treatment period could be too short to observe changes in plasmatic aldosterone levels.

## CONCLUSION

The SAPAAD study is a prospective diagnostic cohort study powered to assess the diagnostic accuracy of a specific algorithm provided by a new generation of PM for the diagnosis of severe SA. This study aims to highlight a correlation between plasma aldosterone level and SA occurrence, severity but also improvement after treatment. The study also evaluates diagnostic accuracy of the algorithm for the diagnosis of moderate SA, characteristics of SA among patients with diastolic dysfunction, related arrhythmias and the potential use of the PM algorithm as a monitoring test for CPAP treated patients.

## STATUS

The study is ongoing. 30 patients have been recruited since June 2016.

## ABBREVIATIONS

AF: atrial fibrillation

AHI: apnea hypopnea index

ACSS: attended cardiorespiratory sleep study

CPAP: continuous positive airway pressure

HF: heart failure

Ea: early diastolic velocity

e-CRF: electronic case report form

LVEF: left ventricular ejection fraction

PM: pacemaker

PSG: polysomnography

RDI: respiratory disturbance index

SA: sleep apnea

SAPAAD: sleep apnea diagnosis using a novel pace-maker algorithm and link with aldosterone plasma level in patients presenting with diastolic dysfunction

SAM: sleep apnea monitoring

Se: sensibility

Sp: specificity

TDI: tissue Doppler imaging

TTE: transthoracic echocardiography

## CONFLICT OF INTEREST

The study is half-funded by Sorin LivaNova.

## AUTHOR'S CONTRIBUTIONS

LCR wrote the manuscript. LCR designed the study with PUM, VF, JNP, PM, JA, AP and ES. RM performed the statistical plan. All authors read and approved the final manuscript.

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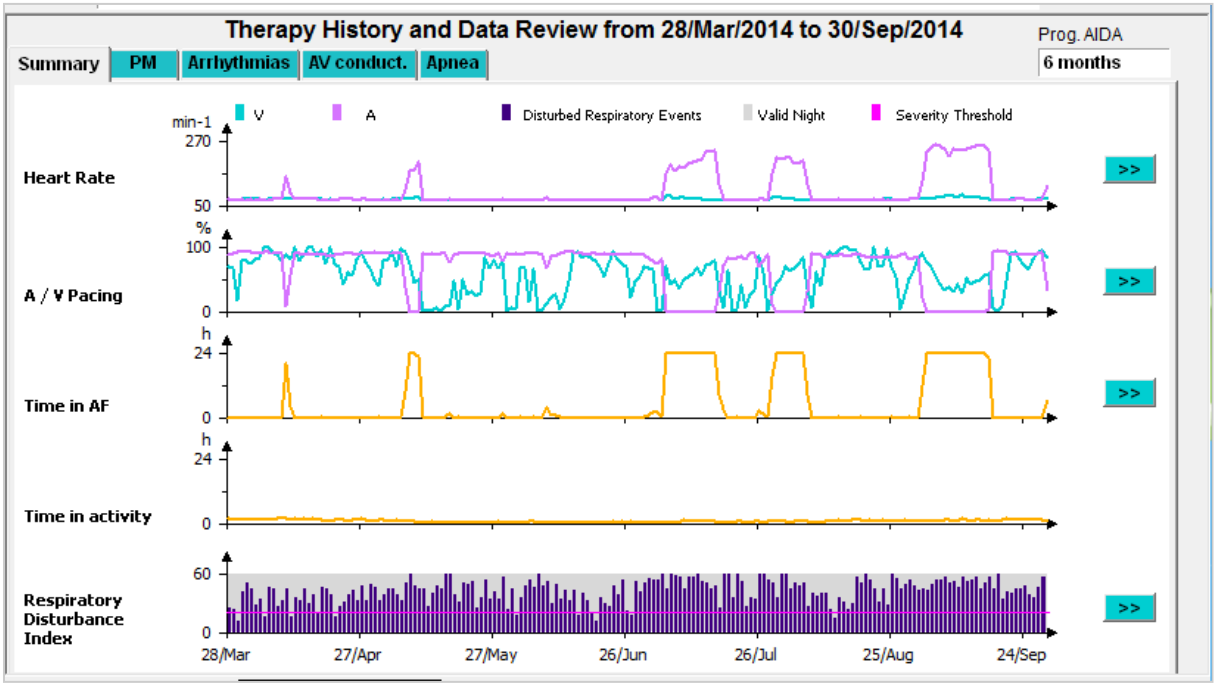
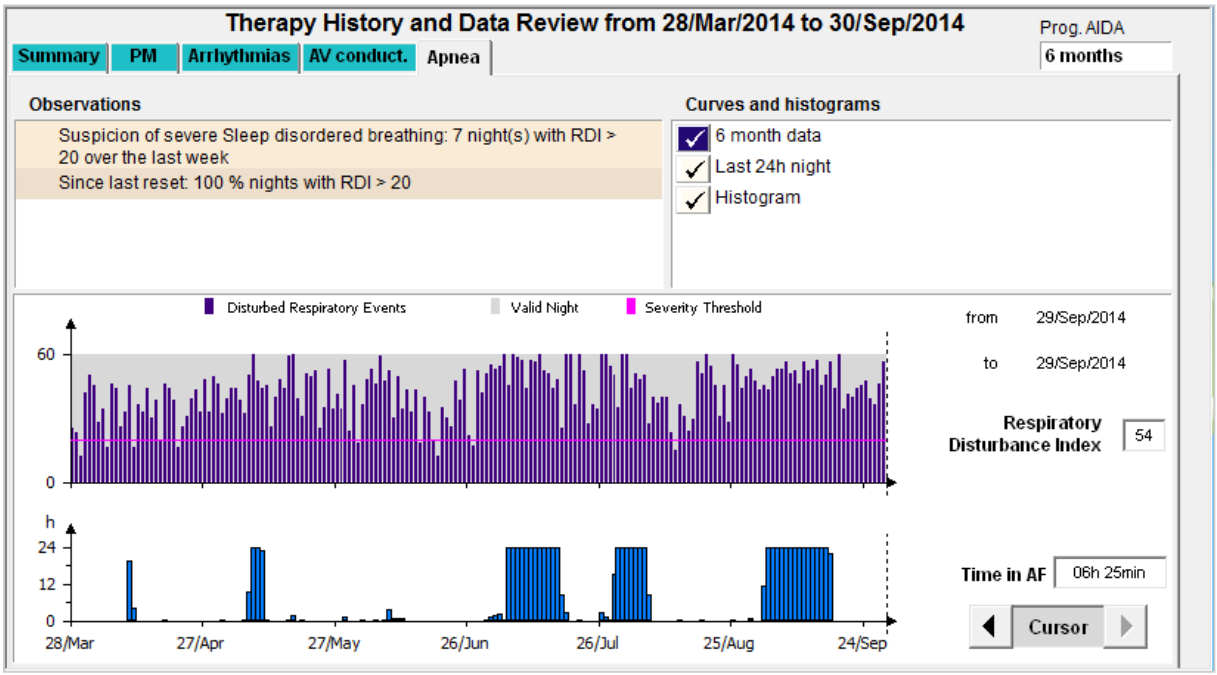
**Additional file 1: Data of the sleep apnea monitoring algorithm available from the pacemaker memories. Print screens from the pacemaker controller.**

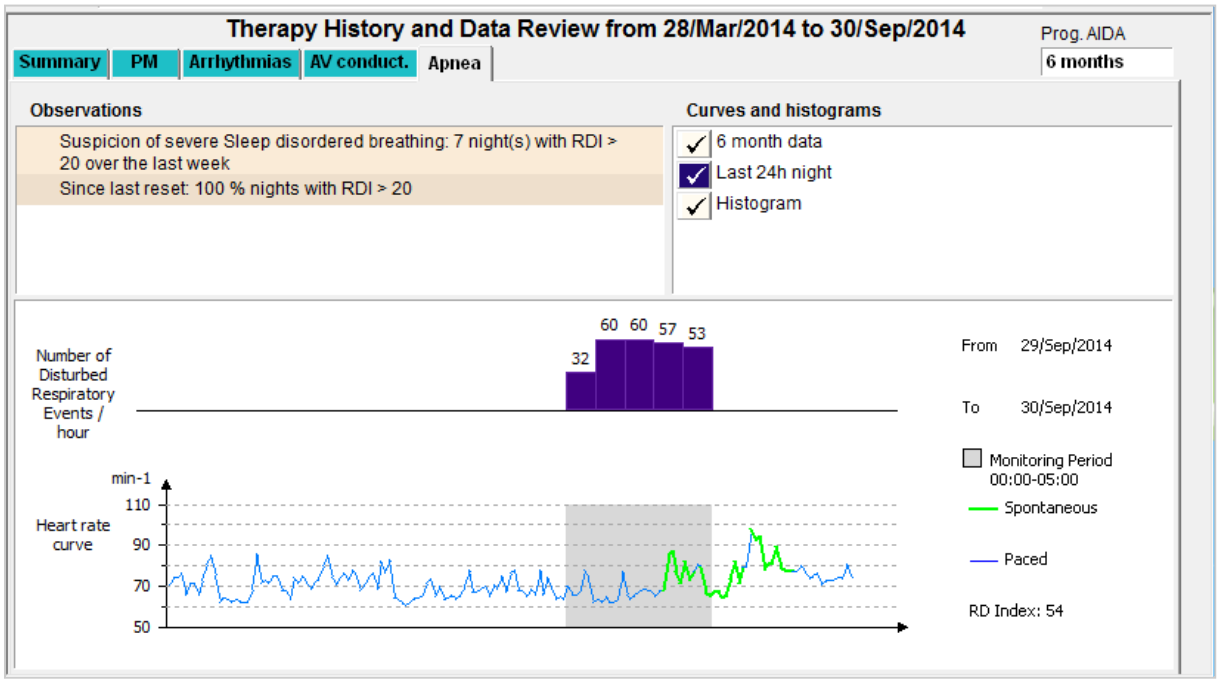
A: Overview of the last six months with corresponding daily data: Heart rate, atrial and ventricular pacing percentages, time in atrial fibrillation, activity and respiratory disturbance index.




B: Overview of the last six months with mean respiratory disturbance index per night (the pink line represents the severity threshold equal to 20) and the corresponding time spent in atrial fibrillation.



C: Overview of the last night with five measures of disturbed respiratory events per hour. The resulting respiratory disturbance index is the mean of these values. The five hours monitoring period is represented by the grey square above the heart rate curve.



**Additional file 2: Epworth sleepiness scale**

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

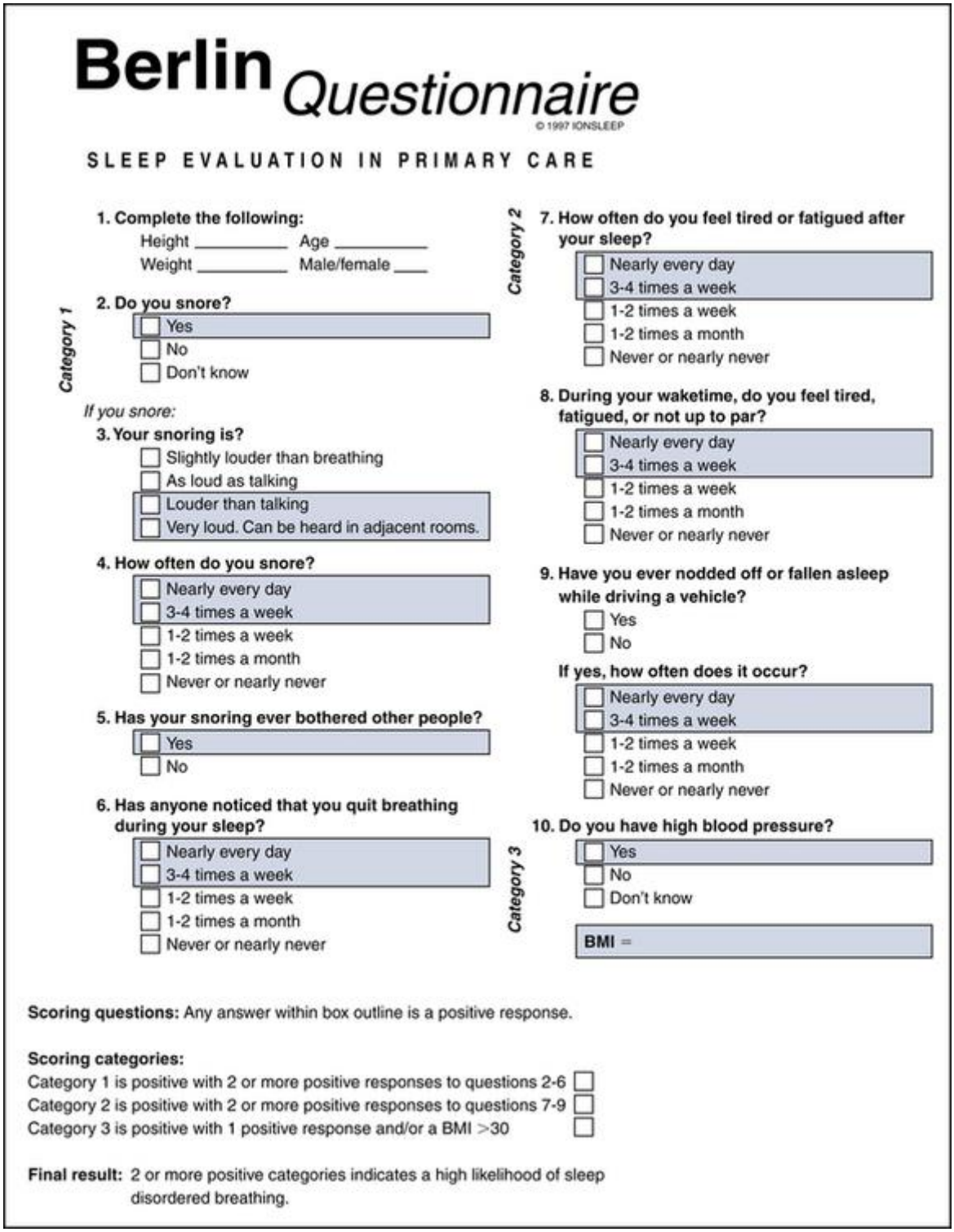
It is important that you answer each question as best you can.

| Situation | Chance of Dozing (0-3) |
|---|---|
| Sitting and reading | |
| Watching TV | |
| Sitting, inactive in a public place (e.g. a theatre or a meeting) | |
| As a passenger in a car for an hour without a break | |
| Lying down to rest in the afternoon when circumstances permit | |
| Sitting and talking to someone | |
| Sitting quietly after a lunch without alcohol | |
| In a car, while stopped for a few minutes in the traffic | |

Results:

- <10: normal range
- 10-12: borderline
- >13: Excessive daytime sleepiness

**Additional file 3: Berlin questionnaire**



# Berlin *Questionnaire*



SLEEP EVALUATION IN PRIMARY CARE

*Category 1*

**1. Complete the following:**

Height _____ Age _____

Weight _____ Male/female ____

**2. Do you snore?**

- ☐ Yes
- ☐ No
- ☐ Don't know

*If you snore:*

**3. Your snoring is?**

- ☐ Slightly louder than breathing
- ☐ As loud as talking
- ☐ Louder than talking
- ☐ Very loud. Can be heard in adjacent rooms.

**4. How often do you snore?**

- ☐ Nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or nearly never

**5. Has your snoring ever bothered other people?**

- ☐ Yes
- ☐ No

**6. Has anyone noticed that you quit breathing during your sleep?**

- ☐ Nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or nearly never

*Category 2*

**7. How often do you feel tired or fatigued after your sleep?**

- ☐ Nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or nearly never

**8. During your waketime, do you feel tired, fatigued, or not up to par?**

- ☐ Nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or nearly never

**9. Have you ever nodded off or fallen asleep while driving a vehicle?**

- ☐ Yes
- ☐ No

**If yes, how often does it occur?**

- ☐ Nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or nearly never

*Category 3*

**10. Do you have high blood pressure?**

- ☐ Yes
- ☐ No
- ☐ Don't know

**BMI =**

**Scoring questions:** Any answer within box outline is a positive response.

**Scoring categories:**

Category 1 is positive with 2 or more positive responses to questions 2-6 ☐

Category 2 is positive with 2 or more positive responses to questions 7-9 ☐

Category 3 is positive with 1 positive response and/or a BMI >30 ☐

**Final result:** 2 or more positive categories indicates a high likelihood of sleep disordered breathing.

## REFERENCES


1. Giordanella J. Rapport sur le thème du sommeil. 2006. http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/064000899.pdf.

2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-1239.

3. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J*. 2008;29(13):1662-1669. doi:10.1093/eurheartj/ehn214.

4. Somers VK, White DP, Amin R, et al. Sleep Apnea and Cardiovascular Disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *J Am Coll Cardiol*. 2008;52(8):686-717. doi:10.1016/j.jacc.2008.05.002.

5. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med*. 1999;160(4):1101-1106. doi:10.1164/ajrccm.160.4.9903020.

6. Garrigue S, Pépin J-L, Defaye P, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. *Circulation*. 2007;115(13):1703-1709. doi:10.1161/CIRCULATIONAHA.106.659706.

7. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206-1214. doi:10.1056/NEJMoa041832.

8. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res*. 2014;115(1):79-96. doi:10.1161/CIRCRESAHA.115.302922.

9. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289(2):194-202.

10. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19):1378-1384. doi:10.1056/NEJM200005113421901.

11. Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. *Am J Hypertens*. 2014;27(8):1069-1078. doi:10.1093/ajh/hpu023.

12. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2007;3(7):737-747.

13. Defaye P, Pépin J-L, Poezevara Y, et al. Automatic recognition of abnormal respiratory events during sleep by a pacemaker transthoracic impedance sensor. *J Cardiovasc Electrophysiol*. 2004;15(9):1034-1040. doi:10.1046/j.1540-8167.2004.04030.x.

14. Defaye P, de la Cruz I, Martí-Almor J, et al. A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. *Heart Rhythm Off J Heart Rhythm Soc*. 2014;11(5):842-848. doi:10.1016/j.hrthm.2014.02.011.

15. Scharf C, Cho YK, Bloch KE, et al. Diagnosis of sleep-related breathing disorders by visual analysis of transthoracic impedance signals in pacemakers. *Circulation*. 2004;110(17):2562-2567. doi:10.1161/01.CIR.0000145540.36097.EB.

16. Shalaby A, Atwood C, Hansen C, et al. Feasibility of automated detection of advanced sleep disordered breathing utilizing an implantable pacemaker ventilation sensor. *Pacing Clin Electrophysiol PACE*. 2006;29(10):1036-1043. doi:10.1111/j.1540-8159.2006.00496.x.

17. Aimé E, Rovida M, Contardi D, et al. Long-term screening for sleep apnoea in paced patients: preliminary assessment of a novel patient management flowchart by using automatic pacemaker indexes and sleep lab polygraphy. *Heart Lung Circ*. 2014;23(10):943-950. doi:10.1016/j.hlc.2014.04.001.

18. Dias M, Gonçalves I, Amann B, et al. Utility of new-generation pacemakers in sleep apnea screening. *Sleep Med*. 2017;37:27-31. doi:10.1016/j.sleep.2017.06.006.

19. Padeletti M, Vignini S, Ricciardi G, et al. Sleep disordered breathing and arrhythmia burden in pacemaker recipients. *Pacing Clin Electrophysiol PACE*. 2010;33(12):1462-1466. doi:10.1111/j.1540-8159.2010.02881.x.

20. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207. doi:10.7326/0003-4819-158-3-201302050-00583.

21. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2013;15(8):1070-1118. doi:10.1093/europace/eut206.

22. Escourrou P, Meslier N, Raffestin B, et al. [Which clinical approach and which diagnostic procedures for obstructive sleep apnea syndrome?]. *Rev Mal Respir*. 2010;27 Suppl 3:S115-123. doi:10.1016/S0761-8425(10)70017-6.

23. Pietzsch JB, Garner A, Cipriano LE, Linehan JH. An integrated health-economic analysis of diagnostic and therapeutic strategies in the treatment of moderate-to-severe obstructive sleep apnea. *Sleep*. 2011;34(6):695-709. doi:10.5665/SLEEP.1030.

24. Zou GY. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. *Stat Med*. 2012;31(29):3972-3981. doi:10.1002/sim.5466.

25. Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS Med*. 2014;11(2):e1001599. doi:10.1371/journal.pmed.1001599.

26. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053. doi:10.1016/S0140-6736(05)71141-7.

27. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353(19):2025-2033. doi:10.1056/NEJMoa051001.

28. Kim SH, Cho G-Y, Shin C, et al. Impact of obstructive sleep apnea on left ventricular diastolic function. *Am J Cardiol*. 2008;101(11):1663-1668. doi:10.1016/j.amjcard.2008.01.056.

29. Arias MA, García-Río F, Alonso-Fernández A, Mediano O, Martínez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. *Circulation*. 2005;112(3):375-383. doi:10.1161/CIRCULATIONAHA.104.501841.

30. Butt M, Dwivedi G, Shantsila A, Khair OA, Lip GYH. Left ventricular systolic and diastolic function in obstructive sleep apnea: impact of continuous positive airway pressure therapy. *Circ Heart Fail*. 2012;5(2):226-233. doi:10.1161/CIRCHEARTFAILURE.111.964106.

31. Lin Y-H, Wang S-M, Wu V-C, et al. The association of serum potassium level with left ventricular mass in patients with primary aldosteronism. *Eur J Clin Invest*. 2011;41(7):743-750. doi:10.1111/j.1365-2362.2010.02462.x.

32. Hung C-S, Chou C-H, Wu X-M, et al. Circulating tissue inhibitor of matrix metalloproteinase-1 is associated with aldosterone-induced diastolic dysfunction. *J Hypertens*. 2015;33(9):1922-1930; discussion 1930. doi:10.1097/HJH.0000000000000619.

33. Sim JJ, Yan EH, Liu ILA, et al. Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population. *J Hypertens*. 2011;29(8):1553-1559. doi:10.1097/HJH.0b013e3283492219.

34. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*. 2007;131(2):453-459. doi:10.1378/chest.06-1442.

35. Gonzaga CC, Gaddam KK, Ahmed MI, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2010;6(4):363-368.

36. Barceló A, Piérola J, Esquinas C, et al. Relationship between aldosterone and the metabolic syndrome in patients with obstructive sleep apnea hypopnea syndrome: effect of continuous positive airway pressure treatment. *PloS One*. 2014;9(1):e84362. doi:10.1371/journal.pone.0084362.

**Usefulness of sleep apnea monitoring by pacemaker sensor in elderly patients with diastolic dysfunction : the SAPAAD Study**

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## ABSTRACT

**Introduction**: Automated detection of sleep apnea (SA) by pacemaker (PM) impedance sensor has been proposed and exhibited good agreement with polysomnography to detect severe SA. The aim of our study was to compare the PM Respiratory Disturbance Index (RDI) and the Apnea Hypopnea Index (AHI) recorded during an attended sleep study with portable monitor, and their correlation with plasma aldosterone levels in a population of patients with diastolic dysfunction.

**Methods:** Consecutive patients referred to the Caen University Hospital for PM implantation presenting isolated diastolic dysfunction were eligible for the study. The primary objective was to evaluate the diagnostic performance of the RDI, and of the mean value over a month (RDIm), compared to the AHI for the diagnosis of severe SA.

**Results:** Among the 349 patients referred to Caen University Hospital for a PM implantation between May 2016 and December 2018, 68 patients were recruited. 63 patients underwent ACSS and were included in the outcomes analysis: 57 presented SA (83.8%), including 16 with severe SA (23.5%), but finally only 8 were treated with continuous positive airway pressure (CPAP). We found the RDI cut-off value of 22 events/h to predict severe SA, with 71.4% sensitivity and 65.2%, specificity. The RDIm cut-off value to detect severe SA was 19 events/h, with a sensitivity of 60% and a specificity of 66%. There was a significant reduction in RDI (p=0.041), RDIm (p=0.039) and AHI (p=0.002) after CPAP treatment. Plasma aldosterone levels, significantly decreased after CPAP treatment. There was a trend toward higher E wave and lateral E/e' ratio in patients with severe SA but body mass index was the only independent predictive factor of severe SA. Supraventricular arrhythmias were frequent in all patients, regardless of SA severity, considering either episodes occurrence or total atrial fibrillation burden.

**Conclusion:** In a population of patients requiring PM implantation with diastolic dysfunction, the SAM algorithm was able to detect severe SA and moderate to severe SA, with good

diagnostic performance values, but also to provide follow-up data for the patients treated with CPAP.

**KEY WORDS:** Sleep apnea, pacemaker, Apnea hypopnea index, Respiratory disturbance index, Continuous positive airway pressure

## INTRODUCTION

Sleep apnea (SA) syndrome, whether obstructive or central, is commonly associated with cardiovascular diseases such as coronary arterial disease, hypertension, diastolic dysfunction (DD), atrial fibrillation (AF) and heart failure. Sleep-disordered breathing has been recognized as a risk factor for these different conditions, and associated with worse prognosis. Nevertheless, the availability of diagnostic tests performed in sleep laboratory is limited and SA is often under recognized. (1) SA prevalence is particularly high among pacemaker (PM) recipients, who are usually less symptomatic than general population. (2) Automated detection of SA, using PM impedance sensor, has been proposed, and exhibited a good agreement with the polysomnography (PSG) to detect severe SA. (3,4) Besides, patients who are candidates to PM implantation are likely to present DD, which is often the first step toward heart failure with preserved ejection fraction (HFpEF). SA diagnosis and treatment are particularly important in this particular clinical form of heart failure, as the drugs with proven benefits in heart failure with reduced ejection fraction failed to improve prognosis of patients with HFpEF. New strategies are based on targeted therapies tailored for the different patients' phenotypes, and sleep-disordered breathing is one of them. (5) The aim of our study was to compare the Respiratory Disturbance Index (RDI) recorded by the PM and the Apnea Hypopnea Index (AHI) obtained from attended cardiorespiratory sleep study (ACSS) with type 3 portable monitor, realized two months after PM implantation, in a population of patients presenting with DD.

## METHODS

We designed a prospective, single-center study, that was approved by the ethics committee (CPP Nord-Ouest III) and the Agence Nationale de Sécurité du Médicament (Register number: 2016-A00034-47). The SAPAAD (Sleep Apnea diagnosis using a novel Pacemaker Algorithm and link with Aldosterone plasma level in patients presenting with Diastolic dysfunction) study was registered on the ClinicalTrials.gov website with trial identification number NCT02751021.

The SAPAAD study follows the SPIRIT guidelines. (6) All patients provided, prior to their enrollment, written informed consent for the study participation, use and disclosure of their information in publications. The detailed methodology of the study was previously published. (7)

**Study population**

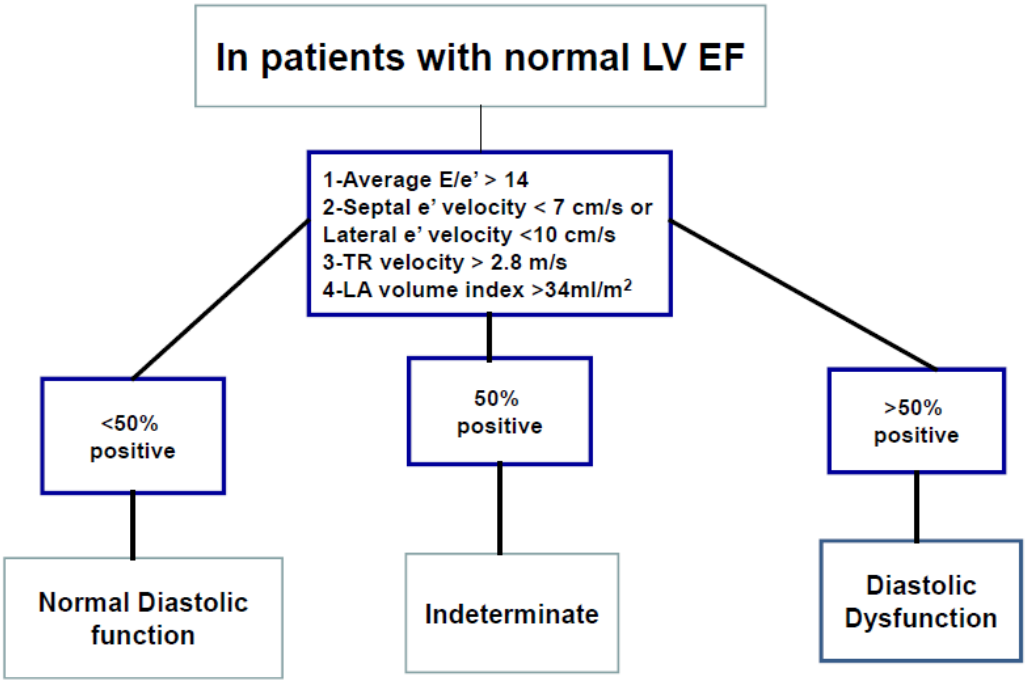
Consecutive patients referred to the Caen University Hospital with clinical and electrical indication for permanent cardiac pacing, according to the current European guidelines, were screened. (8) Patients with DD diagnosed at the pre-implantation transthoracic echocardiography (TTE) were eligible for the study. Patients fulfilling one of these criteria were excluded: younger than 18 years old, lack of informed consent, indication for cardiac resynchronization or left ventricular ejection fraction lower than 45%, indication for epicardial PM, SA treated by continuous positive airway pressure (CPAP), hypertrophic cardiomyopathy, previous mitral valve surgery, heart transplantation.

**Transthoracic echocardiography**

All patients underwent a TTE before PM implantation, using Epic 7® (Philips Healthcare, Amsterdam, Netherlands), during left lateral decubitus, with simultaneous electrocardiogram monitoring. Left ventricular ejection fraction was measured by biplane Simpson method. Diastolic function was assessed using the updated American Society of Echocardiography definition, and classified as normal, grade 1, 2, or 3 of DD, based on left atrium index volume, E wave velocity, lateral and mitral e' velocity, lateral and septal E/e' ratios, tricuspid regurgitation systolic velocity (Figure 1). (9)

**Figure 1: Algorithm for diagnosis of diastolic dysfunction in patients with normal left ventricular ejection fraction**

Printed from Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. (9)
LA : left atrium ; LVEF : left ventricular ejection fraction ; TR : tricuspid regurgitation




**PM implantation**

The patients were implanted with KORA™ 100 or 200, either single or double room (Sorin Livanova, Clamart, France) according to current guidelines and local standard of care. The Sleep Apnea Monitoring (SAM) algorithm uses a rate-responsive sensor, providing an index of minute ventilation derived from measurements of real-time transthoracic impedance variation. SAM thus detects two types of events: apneas (absence of significant respiratory cycle for more than 10 seconds) and severe hypopneas (50% or more decrease in minute ventilation compared to the mean value over the last breathing period sustained for more than 10 seconds). These events are recorded during five hours, generally from 00.00 to 05.00, and

reported with the RDI, which is the average number of events (apnea or hypopnea) detected per hour of estimated sleep. (4)

**Attended cardiorespiratory sleep study**

The ACSS was conducted two months after PM implantation in our sleep laboratory, using a type 3 portable monitor (CID 102L, Cidelec, France). Recorded signals were: nasal flow, pulse oxymetry, respiratory inductance plethymosgraphy, brightness, supra sternal pressure, body position, actimetry, and analysis of respiratory sounds. All the recordings were analyzed by a practitioner graduated with a board certification in sleep medicine, blinded to the RDI value. Mild SA was defined by an AHI between five and 14 events per hour, moderate SA by an AHI between 15 and 29 per hour, and severe SA by an AHI ≥30 events per hour.

**SA treatment**

A specific treatment with nocturnal CPAP ventilation was proposed to all the patients with a a diagnosis of severe obstructive SA. If central mechanism was mainly responsible for SA, the type of ventilation could be different, for example adaptative servo-ventilation, and patient was excluded from this part of the analysis. Two months after the beginning of CPAP therapy, AHI was assessed during ambulatory sleep study using the same model of portable monitor.

**PM follow-up**

At two and six months after hospital discharge, all patients underwent a follow-up visit with clinical examination and device control. The SAM data were collected : the RDI value of the ACSS night, and all the 30 values recorded during the previous month. The mean monthly value of the RDI was manually calculated and named RDIm. AF was defined as supraventricular episodes lasting at least 30 seconds.

**SA clinical evaluation**

The Epworth clinical scale and the Berlin questionnaire were performed prior to PM implantation in order to estimate a pre-test probability of SA, and repeated at two and six months.

**Plasma aldosterone level measurement**

Blood samples were collected between 8 and 10 am, with the patients resting quietly in a semi-recumbent position, during the two-months visit, and at six-months for patients treated with CPAP. They were centrifugated within 30 minutes, and 1-mL plasma aliquots were immediately frozen, and stored at −80°Celsius. Plasma aldosterone concentrations were measured with a commercially available radioimmunoassay kit (Beckman Coulter Immunotech, France).

**Study endpoints and statistical analysis**

The primary objective was to evaluate the diagnostic performance of the SAM algorithm compared to a standard ACSS by using two different approaches:

1/ a “single night” approach, which compared the RDI to the AHI for the diagnosis of severe SA

2/ a “month” approach, which compared the RDIm to the AHI for the diagnosis of severe SA.

Secondary objectives were: evolution of the RDI with CPAP treatment; correlation between plasma aldosterone levels; diagnostic accuracy of the RDI compared to the AHI for the diagnosis of moderate to severe SA; characteristics of SA among patients with diastolic dysfunction; predictive factors of SA. The continuous quantitative variables were expressed by mean and standard deviation and qualitative variables by the number of patients and percentages. The agreement between RDI and AHI for the detection of SA was evaluated by

by the intraclass correlation coefficient (ICC) with 95% confidence interval (CI) and the Bland and Altman method. The diagnostic performance of the SAM algorithm for severe, and moderate to severe (15≤AHI events per hour) SA diagnosis, was evaluated by calculating the area under the Receiver Operator Characteristic (ROC) curve (AUC). To highlight an ICC between the RDI and the AHI of at least 0.80, with an alpha risk equal to 5% and 90% power, 63 patients had to be recruited. We planned therefore to recruit 68 patients, considering that about 5% of the patients would have missing data. The significance level used was $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows version 23.0 (released 2015, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

## RESULTS

### Study population

From May 2016 until December 2018, 349 patients were referred to Caen University Hospital for a PM implantation. Among them, 155 were screened for DD by TTE, in order to recruit the 68 patients required. Patients characteristics of the study population are detailed in Table 1. DD grading was not possible in case of AF at the time of echocardiography, thus only 61 patients were classified: the majority of them presented grade 1 DD (61.8%), 23.5% had grade 2 DD, and only 3 patients had a restrictive profile (4.4%). At two months, 63 patients underwent ACSS and were included in the outcomes analysis, 57 presented SA (83.8%), 22 (32.4%) were classified mild SA, 19 (27.9%) moderate SA and 16 severe SA (23.5%). Finally, only 8 patients were treated with CPAP and had a control ambulatory AHI recording, with aldosterone assessment after two months of treatment (Figure 2).

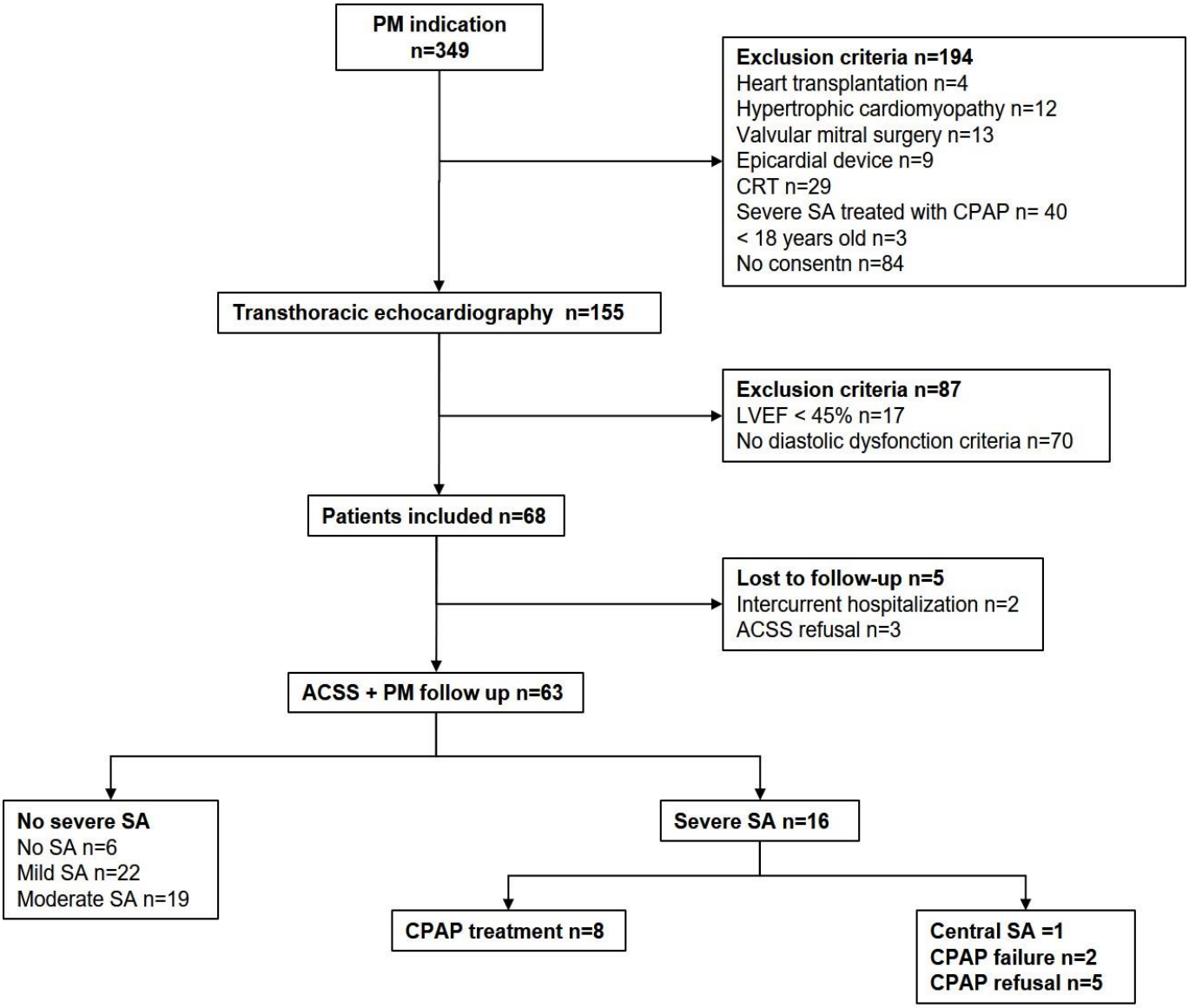
**Table 1 : Study population**

AF : atrial fibrillation; BMI : body mass index ; LA : left atrium; LVEF : left ventricular ejection fraction

| | **Study population n=68** |
|---|---|
| **Age, years** | 80.4±8.2 |
| **BMI, kg/m²** | 26.6±4.6 |
| **Male gender, n(%)** | 41 (60.3) |
| **Diabetes mellitus, n(%)** | 20 (29.4) |
| **Hypertension, n(%)** | 57 (83.8) |
| **Dyslipidemia, n(%)** | 45 (66.2) |
| **Smoking, n(%)** | 25 (36.8) |
| **Alcohol, n(%)** | 19 (27.9) |
| **Coffee/Tea, n(%)** | 41 (60.3) |
| **Coronary artery disease, n(%)** | 21 (30.9) |
| **AF, n(%)** | 20 (29.4) |
| **Valvular disease, n(%)** | 15 (22.1) |
| **Cardiac surgery, n(%)** | 17 (25) |
| **Pulmonary disease, n(%)** | 4 (5.9) |
| **LVEF, %** | 61.5±7.2 |
| **LA volume, ml/m²** | 48.4±11.5 |
| **E/A** | 1±0.6 |
| **Lateral E/e'** | 11.1±4.2 |
| **Septal E/e'** | 13.6±5.1 |
| **Diastolic dysfunction, n(%)** | n=61 |
| grade 1 | 42 (61.8) |
| grade 2 | 16 (23.5) |
| grade 3 | 3 (4.4) |

**Figure 2 : Study flow chart**

ACSS : attended cardiorespiratory sleep study; CPAP : continuous positive airway pressure; LVEF : left ventricular ejection fraction; PM : pacemaker; SA : sleep apnea




**RDI, RDIm and AHI**

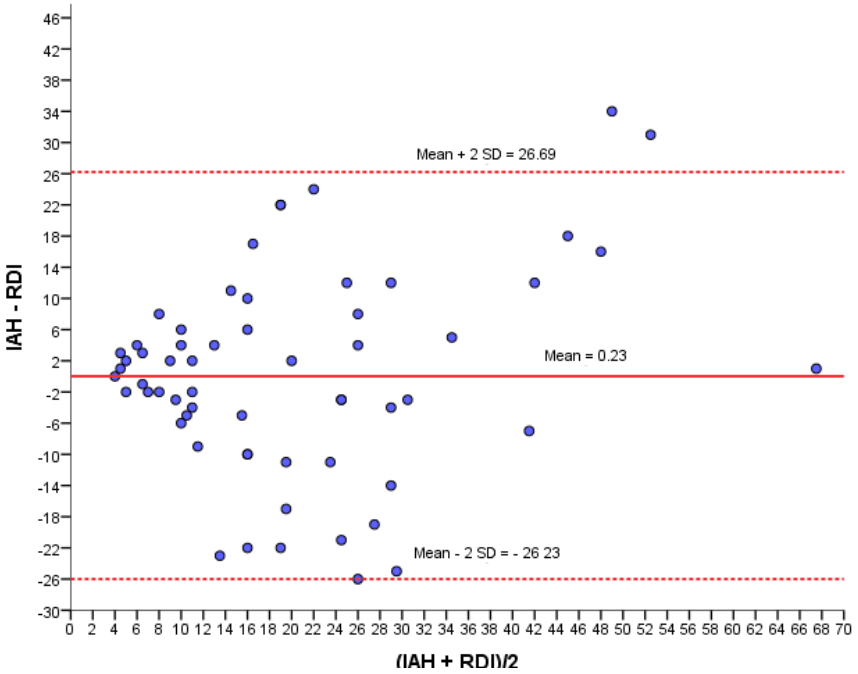
As expected, RDI and RDIm exhibited high correlation with an ICC =0.80 (95% confidence interval [CI] 0.66-0.88, p<0.001). RDI and AHI were also significantly correlated with an ICC=0.76 (95% CI 0.60-0.86, p<0.001) and a mean bias by the Bland and Altman analysis of 0.2±13.2 events/h. Finally, RDIm and AHI were significantly correlated, ICC= 0.61 (95% CI 0.35-0.76, p<0.001) and mean difference of 2.1±15.1 events/h (Figure 3).

**Figure 3 : Bland-Altman plots for severe sleep apnea detection showing mean of the differences (bias) presented with 2 standard derivation interval**

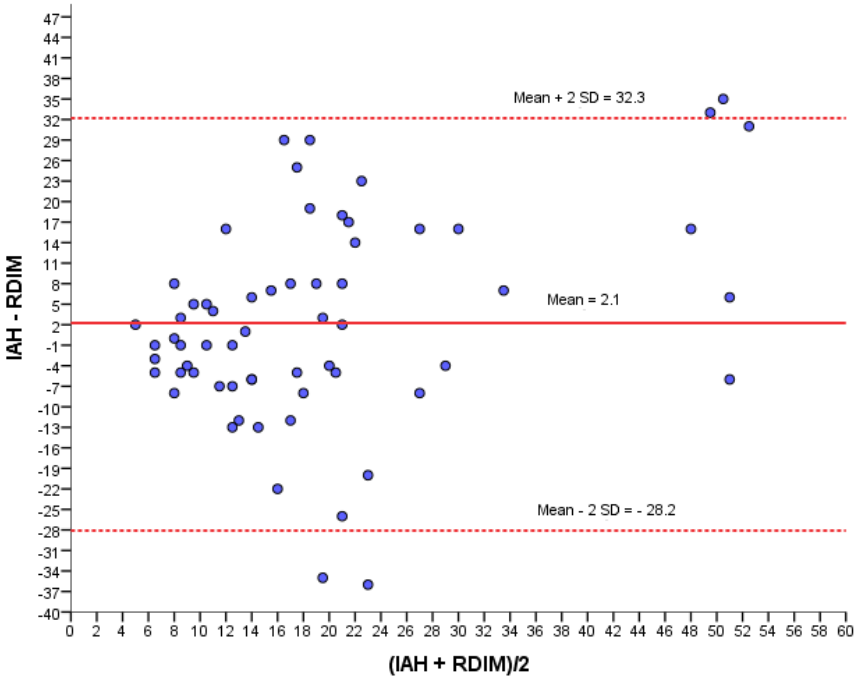
a: RDI and AHI; b: RDIm and AHI, c: RDI and RDIm

Y axis: difference between the indexes; X axis: mean value of the indexes

**a:**




**b:**



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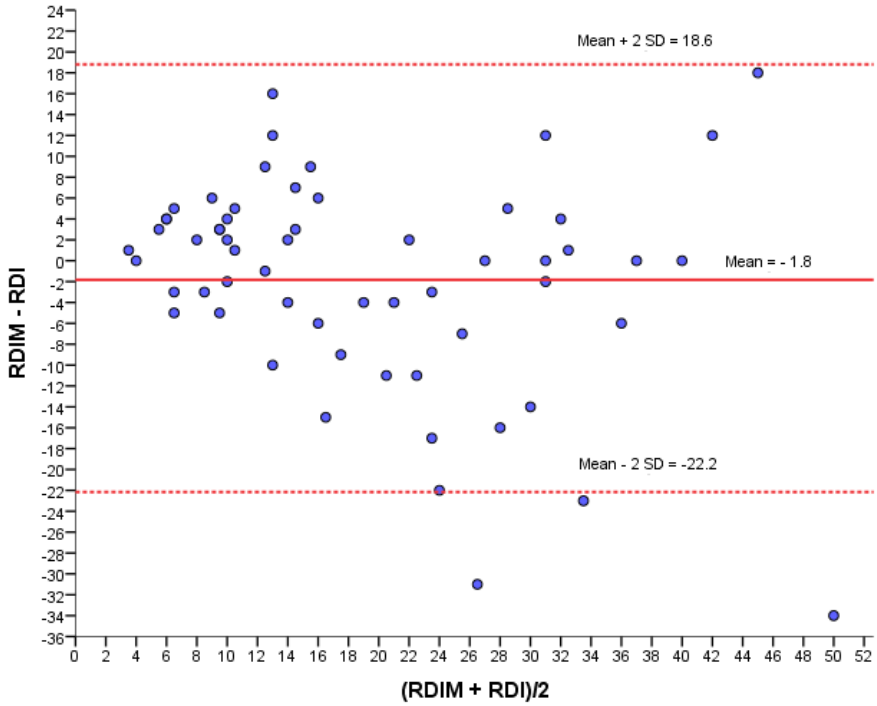



**Primary endpoint**

*Night approach*

By ROC curves analysis, the AUC of the RDI was 0.75±0.08 (95%CI 0.59-0.91, p=0.007). We found a RDI cut-off value of 22 events/h to predict severe SA, which yielded a sensitivity of 71.4%, a specificity of 65.2%, a positive predictive value (PPV) of 38.5%, and a negative predictive value (NPV) of 88.2%.

*Monthly approach*

The AUC of the RDIm was 0.73±0.09 (95% CI 0.56-0.91, p=0.011). The RDIm cut-off value to detect severe SA was 19 events/h, with a sensitivity of 60%, a specificity of 66%, a PPV of 36%, and a NPV of 83.8%. ROC curves are shown in Figure 4 and diagnostic performance analyses are detailed in Table 2.

**Table 2 : Diagnostic performance of RDI and RDIm to detect severe sleep apnea**

RDI : respiratory disturbance index; RDIm : respiratory disturbance index monthly

| | | RDI | | RDIm | |
|---|---|---|---|---|---|
| **Statistic** | **Formula** | **Value** | **95% CI** | **Value** | **95% CI** |
| Sensitivity | $\frac{a}{a+b}$ | 71.43% | 41.90% to 91.61% | 60.00% | 32.29% to 83.66% |
| Specificity | $\frac{d}{c+d}$ | 65.22 % | 49.75% to 78.65% | 65.96 % | 50.69% to 79.14% |
| Positive Likelihood Ratio | $\frac{Sensitivity}{1-Specificity}$ | 2.05 | 1.23 to 3.44 | 1.76 | 0.99 to 3.13 |
| Negative Likelihood Ratio | $\frac{1-Sensitivity}{Specificity}$ | 0.44 | 0.19 to 1.03 | 0.61 | 0.32 to 1.17 |
| Disease prevalence | $\frac{a+b}{a+b+c+d}$ | 23.33% (*) | 13.38% to 36.04% | 24.19% (*) | 14.22% to 36.74% |
| Positive Predictive Value | $\frac{a}{a+c}$ | 38.46% (*) | 27.17% to 51.15% | 36.00% (*) | 24.07% to 49.96% |
| Negative Predictive Value | $\frac{d}{b+d}$ | 88.24 % (*) | 76.14% to 94.63% | 83.78 % (*) | 72.89% to 90.85% |
| Accuracy | $\frac{a+d}{a+b+c+d}$ | 66.67% (*) | 53.31% to 78.31% | 64.52% (*) | 51.34% to 76.26% |

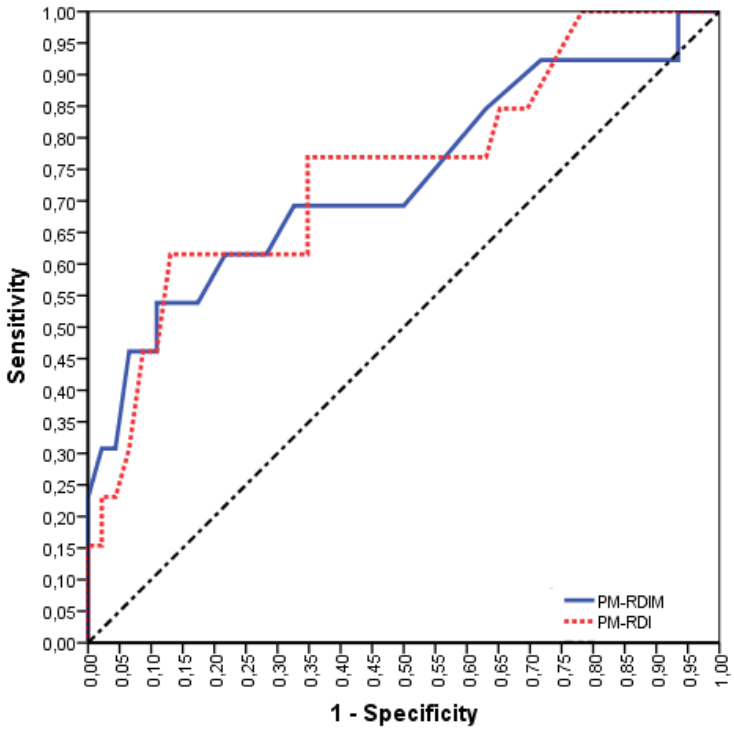
**Secondary endpoints**

*SAM for monitoring CPAP treatment*

Only 8/16 patients with diagnosed severe SA were successfully treated with CPAP and underwent a control ambulatory sleep study. There was a significant reduction in RDI (p=0.041), RDIm (p=0.039) and AHI (p=0.002) after two months of CPAP treatment. Considering the other polygraphic data, we observed a significant improvement in minimum oxygen saturation (p=0.011), a reduction of the time spent with a saturation below 90% (p=0.046), and a trend toward a higher mean oxygen saturation (p=0.054). Conversely, there was no improvement in the Berlin Questionnaire or the Epworth score. Similarly, we did not report any change in pacing data or AF burden. All characteristics of patients treated with CPAP are shown in Table 3.

**Figure 4: ROC curves of the diagnostic performance of RDI and RDIm to detect severe (panel a) and moderate to severe (panel b) sleep apnea**

**a:**




**b:**

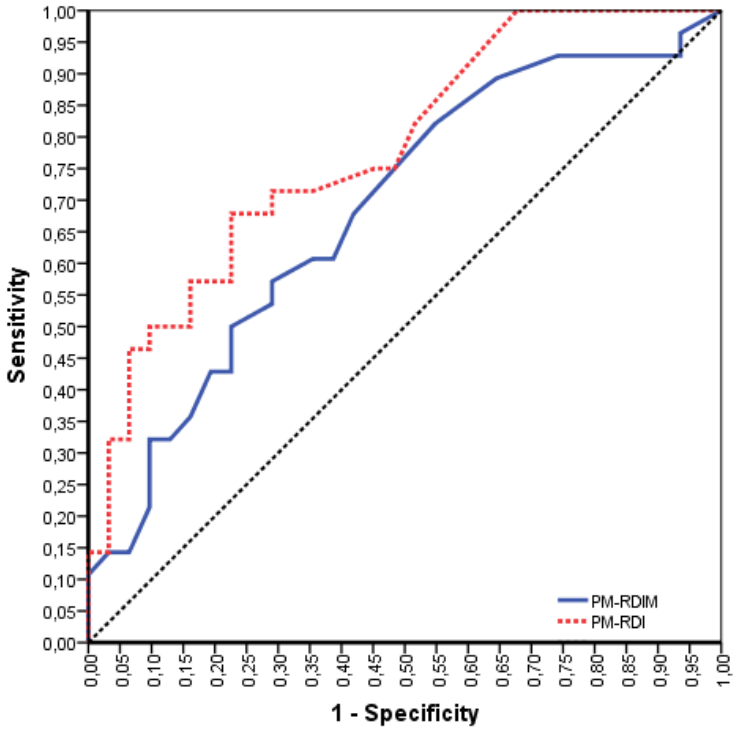


**Table 3 : Characteristics of patients before and after one month of CPAP treatment**

AF: atrial fibrillation; AHI: apnea hypopnea index; bpm: beat per minute; ESS: Epworth Sleepiness Scale; RDI: respiratory disturbance index; RDIm: respiratory disturbance index of the month; SV: supraventricular

| | No severe SA n=47 | Severe SA n=16 | p | CPAP treatment n=8 | p before/after CPAP |
|---|---|---|---|---|---|
| **RDI, events/h** | 17.2±11.3 | 29.6±16.2 | 0.002 | 12.7±5.8 | 0.041 |
| **RDIm, events/h** | 16.3±9.0 | 24.2±16.5 | 0.02 | 19.9±14.3 | 0.039 |
| **AHI, events/h** | 12.8±7.1 | 43.1±15.6 | <0.001 | 11.1±9.1 | 0.002 |
| **Mean Oxygen saturation, %** | 92.8±1.5 | 91.9±2.4 | 0.082 | 94±1.3 | 0.054 |
| **Minimum Oxygen saturation, %** | 83.2±4.3 | 74.9±9.1 | <0.001 | 83.9±3.9 | 0.011 |
| **Oxygen saturation <90%, % of time** | 6.5±11.5 | 20.1±22.9 | 0.004 | 6.5±11.5 | 0.048 |
| **Oxygen saturation <85%, % of time** | 0.2±0.5 | 2.8±4.30 | <0.001 | 0.2±0.5 | 0.042 |
| **Berlin score (/3)** | 1.5±0.8 | 1.7±0.5 | 0.304 | 1.5±0.8 | 0.516 |
| **ESS (/24)** | 8.0±4.1 | 9±3.3 | 0.583 | 7.8±3.5 | 0.271 |
| **SV arrhythmia (n=57)** | 31 (68.9) | 9 (75.0) | 0.745 | 5 (62.5) | 0.650 |
| **Nocturnal SV arrhythmia (n=57)** | 19 (42.2) | 5 (41.7) | 1.000 | 2 (25) | 0.328 |
| **Ventricular arrhythmia** | 13 (27.7) | 5 (31.3) | 1.000 | 3 (37.5) | 1.000 |
| **Nocturnal ventricular arrhythmia** | 3 (6.4) | 1 (6.3) | 1.000 | 0 (0) | 0.870 |
| **AF burden, %** | 7.1±20.8 | 1.5±1.4 | 0.276 | 0.4±1.1 | 0.354 |
| **Atrial pacing, %** | 35.4±34.1 | 30.4±31.9 | 0.651 | 40.4±33.8 | 0.128 |
| **Ventricular pacing, %** | 30.3±38.5 | 38.9±41.6 | 0.463 | 34.0±39.2 | 0.468 |
| **Heart rate, bpm** | 72±10 | 74±8 | 0.424 | 70±7 | 0.11 |
| **Nocturnal heart rate, bpm** | 63±5 | 65±7 | 0.312 | 62±5 | 0.102 |

*Plasma aldosterone levels*

Aldosterone levels, measured during the 2-months visit, were a little higher in patients diagnosed with severe SA but the difference was not statistically different. The correlation tests did not show any significant correlation between aldosterone levels and AHI or RDI. Similarly, aldosterone levels were not associated with the severity of the DD, despite slightly higher levels in patients with either grade 2 or 3 DD. Conversely, among the 8 CPAP-treated patients,

aldosterone levels assessed at six months had significantly decreased (231±157pmol/l versus 167±111pmol/l, p=0.034). Aldosterone measures are summarized in Table 4.

**Table 4 : Aldosterone levels**

DD : diastolic dysfunction ; SA : sleep apnea

| | **No severe SA n=45** | **Severe SA n=16** | **p for SA severity** | **Grade 1 DD n=40** | **Grade 2 or 3 DD n=17** | **p for DD grade** |
|---|---|---|---|---|---|---|
| **M2 Aldosterone** | 193±137 | 218±143 | 0,812 | 193±111 | 211±191 | 0,657 |
| | | | **p for M2 vs M6** | | | |
| **M6 Aldosterone** | | 167±111 | 0,034 | | | |

*Performance diagnostic of SAM for moderate to severe SA*

Using the ROC curves analysis, we found the RDI and RDIm cut-off values to predict moderate to severe SA, respectively 18 events/h (AUC=0.78±0.06, p<0.001, sensitivity=72.4%, specificity=67.7%), and 17 events/h (AUC=0.69±0,07, p=0.015, sensitivity=56.7%, Specificity=62.5%). (Figure 4)

*Characteristics of SA*

Patients with severe SA had significantly lower RDI, RDIm, AHI, and minimum oxygen saturation than the others. They spent more time with oxygen saturation below 90% and 85%, but their mean saturation only tended to be lower. Conversely, the results at the Berlin Questionnaire and the Epworth Scale were not different between patients, whether they had severe SA or not, and patients were not very symptomatic. Six patients were in permanent AF and were not analysed for supraventricular arrhythmias occurrence, that were frequent in all

patients, regardless of SA severity, considering either AF episodes occurrence, or total AF burden. There was also no difference in ventricular arrhythmias occurrence. See Table 3 for the description of patients with severe SA.

*Predictive factors of SA*

Patients with severe SA had a higher BMI (30.0±5.0 vs 25.8±4.0 kg/m², p=0.001), a trend toward higher E wave (88.7±25.4 vs 77.1±20.6 cm/s, p=0.079), and lateral E/e' ratio (12.5±4.7 vs 10.6±4.0, p=0.122). In multivariate analysis, BMI was identified as the only independent predictor of severe SA. Although there were more patients with grade 2 or 3 of DD among patients with severe SA, the grade of DD was not significantly associated with severe SA (Table 5). We also analysed clinical and echocardiographic features associated with moderate to severe SA (Table 6). Conversely, diabetics (odds ratio (OR)=5.95, p=0.01), male patients (OR=4.2, p=0.037), with higher E wave (OR= 1.04, p=0.013), were at higher risk to present moderate to severe SA in multivariate analysis.

**Table 5 : Univariate and multivariate of clinical and echographic findings associated with severe SA**

AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; ESS: Epworth Sleepiness Scale; LA: left atrium; LVEF: left ventricular ejection fraction; OR: odds ratio; SA: sleep apnea

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | **Severe SA n=16** | **No severe SA n=47** | **p** | **OR** | **95% CI** | **p** |
| **Age, years** | 78.9±7.5 | 80.2±8.5 | 0.577 | | | |
| **BMI, kg/m²** | 30.0±5.0 | 25.8±4.0 | 0.001 | 1.22 | 1.06-1.41 | 0.006 |
| **BMI≥30, n(%)** | 9 (56.3) | 7 (14.9) | 0.002 | 5.3 | 1.3-21.2 | 0.027 |
| **Male gender, n(%)** | 11 (68.8) | 28 (59.6) | 0.366 | | | |
| **Diabetes mellitus, n(%)** | 7 (43.8) | 13 (27.7) | 0.188 | 0.82 | 0.18-3.67 | 0.793 |
| **Hypertension, n(%)** | 14 (87.5) | 38 (80.9) | 0.428 | | | |
| **Dyslipidemia, n(%)** | 11 (68.8) | 30 (63.8) | 0.485 | | | |
| **Smoking, n(%)** | 6 (37.5) | 18 (38.3) | 0.599 | | | |
| **Alcohol, n(%)** | 3 (18.8) | 16 (34) | 0.204 | | | |
| **Coffee/Tea, n(%)** | 8 (50) | 31 (66) | 0.2 | 1.39 | 0.33-5.91 | 0.649 |
| **CAD, n(%)** | 7 (43.8) | 13 (27.7) | 0.187 | 2.03 | 0.51-8.2 | 0.308 |
| **AF, n(%)** | 5 (31.3) | 14 (29.8) | 0.573 | | | |
| **Valvular disease, n(%)** | 4 (25) | 10 (21.3) | 0.502 | | | |
| **Cardiac surgery, n(%)** | 4 (25) | 13 (27.7) | 0.557 | | | |
| **Berlin score (/3)** | 1.7±0.5 | 1.5±0.7 | 0.304 | | | |
| **ESS (/24)** | 9±3.3 | 8.4±3.7 | 0.584 | | | |
| **LVEF, %** | 61.3±7.5 | 61.7±7.1 | 0.837 | | | |
| **LA volume, ml/m²** | 47.3±9.4 | 47.8±9.6 | 0.853 | | | |
| **E wave, cm/s** | 88.7±25.4 | 77.1±20.6 | 0.079 | 0.99 | 0.94-1.05 | 0.795 |
| **A wave, cm/s** | 104±44.2 | 89.2±31.7 | 0.196 | 1.04 | 0.98-1.07 | 0.69 |
| **Lateral E/e'** | 12.5±4.7 | 10.6±4.0 | 0.122 | 1.08 | 0.93-1.26 | 0.342 |
| **Septal E/e'** | 13.9±7.5 | 13.6±4.2 | 0.915 | | | |
| **Diastolic dysfunction*, n(%)** | n=13 | n=44 | | | | |
| grade 1 | 8 (61.5) | 32 (72.7) | | | | |
| grade 2 | 4 (30.8) | 11 (25) | 0.397 | | | |
| grade 3 | 1 (7.7) | 1 (2.3) | | | | |

**Table 6 : Univariate and multivariate of clinical and echographic findings associated with moderate to severe SA**

AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; ESS: Epworth Sleepiness Scale; LA: left atrium; LVEF: left ventricular ejection fraction; OR: odds ratio; SA: sleep apnea

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | **Moderate to severe SA n=31** | **No or mild SA n=32** | **p** | **OR** | **95% CI** | **p** |
| **Age, years** | 78.3±8.1 | 81.5±8.1 | 0.116 | 0.9 | 0.9-1.0 | 0.361 |
| **BMI, kg/m²** | 28.5±4.4 | 25.3±4.3 | 0.005 | 1.07 | 0.93-1.26 | 0.327 |
| **BMI≥30, n(%)** | 12 (38.7) | 4 (12.5) | 0.022 | 1.66 | 0.36-7.57 | 0.513 |
| **Male gender, n(%)** | 17 (53.1) | 22 (71) | 0.196 | 4.22 | 1.09-16.34 | 0.037 |
| **Diabetes mellitus, n(%)** | 15 (48.4) | 5 (15.6) | 0.007 | 5.95 | 1.53-23.13 | 0.01 |
| **Hypertension, n(%)** | 27 (87.1) | 25 (78.1) | 0.509 | | | |
| **Dyslipidemia, n(%)** | 21 (67.7) | 20 (62.5) | 0.793 | | | |
| **Smoking, n(%)** | 14 (45.2) | 10 (31.3) | 0.305 | | | |
| **Alcohol, n(%)** | 10 (32.3) | 9 (28.1) | 0.788 | | | |
| **Coffee/Tea, n(%)** | 19 (61.3) | 20 (62.5) | 1.000 | | | |
| **CAD, n(%)** | 13 (41.9) | 7 (21.9) | 0.109 | 1.12 | 0.25-5.06 | 0.887 |
| **AF, n(%)** | 7 (22.6) | 12 (37.5) | 0.274 | | | |
| **Valvular disease, n(%)** | 8 (25.8) | 6 (18.8) | 0.556 | | | |
| **Cardiac surgery, n(%)** | 9 (29) | 8 (25) | 0.782 | | | |
| **Berlin score (/3)** | 1.6±0.6 | 1.4±0.7 | 0.169 | 1.84 | 0.69-4.93 | 0.227 |
| **ESS (/24)** | 8.3±3.6 | 8.8±3.7 | 0.558 | | | |
| **LVEF, %** | 60±7 | 63±8 | 0.163 | 0.98 | 0.89-1.07 | 0.596 |
| **LA volume, ml/m²** | 47.6±9.1 | 47.8±10.6 | 0.924 | | | |
| **E wave, cm/s** | 87.0±21.2 | 72.3±21.4 | 0.014 | 1.04 | 1.01-1.07 | 0.013 |
| **A wave, cm/s** | 91.8±40.5 | 92.9±30.2 | 0.908 | | | |
| **Lateral E/e'** | 11.8±4.3 | 10.4±4.2 | 0.190 | 1.03 | 0.78-1.28 | 0.981 |
| **Septal E/e'** | 13.5±5.7 | 13.8±4.6 | 0.792 | | | |
| **Diastolic dysfunction*, n (%)** | n=26 | n=31 | | | | |
| grade 1 | 16 (61.5) | 24 (77.4) | | | | |
| grade 2 | 9 (34.6) | 6 (19.4) | 0.412 | | | |
| grade 3 | 1 (3.8) | 1 (3.2) | | | | |

## DISCUSSION

To our knowledge, this study is the first one that specifically assessed the use of the SAM algorithm in the management of patients with DD. We showed that both RDI and RDIm were suitable for severe SA detection, but also for monitoring of CPAP treatment, and for moderate to severe SA detection. Considering aldosterone levels, we did not report any significant association with neither SA severity nor DD grade, nevertheless they decreased after CPAP treatment. There was a trend toward higher E wave and lateral E/e' ratio in patients with severe SA, but the presence of severe SA was not correlated with DD grade.

Firstly, the RDI was significantly correlated with the AHI with a good agreement between the two measures, as previously reported with the same (4,10,11) or another automated algorithms provided by PMs. (12) Defaye et al. published the first prospective study that

validated this version of the SAM algorithm for severe SA detection, and they found a cut-off value of 20 events/h, with high sensitivity (88.9%) and specificity (84.6%), compared to PSG. Our present cut-off value is a little higher but yielded lower predictive values, respectively 71.4% and 65.2%, compared with the AHI recorded during an ACSS with a type 3 portable monitor. All the previous publications about RDI and AHI comparison used the PSG as reference test. (7) Only one other study compared the RDI and the AHI recorded with portable monitor for diagnosis of SA, defined as AHI >10 events/h. The authors found higher AHI compared to RDI in patients with SA, although the difference was not significant, and they did not compare performance diagnostic values of the different indexes. (13) We sought to compare the SAM algorithm to the ACSS with portable monitor, in order to use a reference test widely available in daily practice, as PSG is at very difficult access in our institution, as in many centres. However, it has been already shown that the portable monitors, even used in attended conditions, are less accurate than the PSG for SA diagnosis, with a frequent under estimation of the AHI, especially because of an under recognition of sleep. A recent meta-analysis of studies comparing level 3 versus level 1 (PSG) sleep studies, reported a summary sensitivity ranged between 0.79 and 0.97, and summary specificity ranged between 0.60 and

0.93, across different AHI cut-off values. (14) Thus, the American Association for Sleep Medicine only recommended portable monitoring for patients with high pre-test probability and no medical comorbidity (i.e. heart failure or respiratory disease), and not for general screening in asymptomatic individuals. (15,16) Therefore, we might assume that the discrepancies between our RDI diagnostic performance values and those previously published are related to the reference test. We also considered an average value of the RDI recording over a month, as already proposed by Aime et al. (10) The RDIm was closely correlated to RDI and exhibited similar diagnostic performance values, when compared to the AHI. Inter-night variability of sleep-disordered breathing has been long recognized, and supported the recommendation to repeat the sleep study in a patient with a high pre-test probability and a non-conclusive AHI. (15) This variability has also been reported in RDI recorded by impedance sensor, with a RDI >20 events/h recorded at least one night in 90% of unselected patients. (17) Therefore, we hypothesized that an average value over a month could be better related to AHI, but this study failed to prove it.

Our study showed for the first time that the RDI can be used to follow CPAP-treated patients. Both RDI and RDIm decreased significantly after two months of treatment. Moreover, we observed inter-night variability of RDI in the treated patients, probably related with CPAP compliance, but we did not retrieve CPAP data in order to test this hypothesis. Thus, it would be interesting to further examine RDI and/or RDIm variations after CPAP treatment. The PM could become an interesting and easy-to-use tool to assess CPAP efficacy and in-home compliance.

We also determined cut-off values of RDI and RDIm to detect moderate to severe SA, as Dias et al. previously did in an unselected population of PM recipients, with a lower threshold value than ours. (11) There is no manufacturer recommended cut-off to predict moderate to severe SA, whereas it could be particularly relevant in this population, with frequent associated cardiovascular diseases, to detect, not only severe, but also moderate SA. In France, CPAP treatment can be proposed to patients with moderate SA in case of cardiovascular

comorbidities, such as resistant hypertension, recurrent AF, heart failure whether with reduced or preserved ejection fraction.

As previously reported, we observed a very high prevalence of SA (84%) in our population, with 51% of the patients with moderate to severe SA. These values are higher than those reported, more than 10 years ago in the first publications about SA detection with PM, (2,3) but comparable with more recent studies. (4,11) We planned to find high prevalence of SA, as we selected patients with both PM and DD. Several reports have already highlighted that SA and DD are often associated, even there are some conflicting data about identification of obstructive SA as an independent risk factor for DD development, because of numerous other associated factors (age, BMI, hypertension, metabolic syndrome). (18) CPAP has been shown to limit progression or even reverse abnormalities in diastolic function. (19) Here, we focused on detecting SA in patients with DD, in order to initiate appropriate treatment, and eventually, to help preventing HFpEF. In a younger population of patients with HFpEF, Bitter et al. reported 69.3% of SA. (20) We did not find a correlation between the severity grades of DD and SA, but a higher E wave was an independent predictor of moderate to severe SA. It is worth to note that, finally, only 44% of the screened patients presented isolated DD (68/155), whereas the prevalence of DD of any grade was almost 70% in patients over 75 years old, in a previous report in the community. (21)

Considering the aldosterone levels, we did not observe a significant correlation with the severity of SA or the grades of DD, as we expected, in line with the published literature. (22,23) However, CPAP treatment significantly decreased plasmatic levels, as it was suggested in a prospective study in patients with SA and resistant hypertension. (24)

Relationship between AF and SA has been described for years: the correlation between severity of SA and AF occurrence, (25) the worse prognosis of AF associated with SA, (26) as well as the poorer results of catheter ablation in case of severe non-treated SA. (27) Thus, this new generation of PM, that is able to provide both data on SA and arrhythmias, are at particular interest. During device follow-up, the SAM algorithm monitoring screen presents a timeline

with daily RDI and AF burden, showing high inter-night variability, as discussed by Moubarak et al. In their study, as in our present work, they were not able to relate AF occurrence to RDI burden or a cut-off value. On the contrary, the very recently published results from the prospective study RESPIRE confirmed that severe SA, diagnosed by the SAM algorithm, was associated with almost the double risk of significant AF, defined as cumulative AF episodes lasting ≥24 hours over two consecutive days, and with an increased risk of persistent AF. (28)

Those old patients with DD, who received PM, are at high risk of SA and related AF, and these comorbidities are additional risk factors for HFpEF. Therefore, a simple automated diagnostic tool, as the SAM algorithm, providing long term surveillance, could help clinicians to early diagnose and if possible, treat those associated conditions. Whether we should use lower cut-off values in these patients, with cardiovascular diseases to detect moderate to severe SA, should be addressed by further studies. Conversely, in the patients with low RDI over long term, severe SA could be ruled out and these patients not proposed for sleep study.

**Study limitations**

Limitations of our study include the patient number, particularly for the analysis of CPAP-treated patients. We had to face a high percentage of patients' refusal to participate, to complete ACSS, or to try the CPAP treatment. These patients were old, with very few symptoms, and therefore unwilling to do extra visits. Finally, this limit underlines the importance of automated screening tools, as the SAM algorithm. We used as reference test the AHI recorded during ACSS with type 3 portable monitor, which is not the gold standard for SA diagnosis, but already an alternative test, and this could have induced systematic bias. We explored the RDIm diagnostic performance, as this monthly mean value could counterbalance the inter night variability of RDI, but with no improved results. This could be explained by the comparison with a single AHI measure, also known to be highly variable. Besides, some patients had invalid nights for RDI analysis, that could have led to underpower the RDIm diagnostic performance. Confusing factors for aldosterone levels, like medications interacting

with renine angiotensine aldosterone system, were not analysed, in order to explain the lack of correlation with SA severity.

## CONCLUSION

In a population of patients with DD requiring PM implantation, the RDI, and its monthly mean value, are able to detect severe SA and moderate to severe SA, with good diagnostic performance values, but also to provide follow-up data for the patients treated with CPAP. The SAM algorithm is thus helpful to early diagnose SA, which could precipitate, in these high-risk patients, further heart failure progression.

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## AUTHORS CONTRIBUTION

LCR wrote the manuscript. LCR designed the study with PUM, VF, ALC, JNP, PM, and ES. RM and LCR performed the statistical plan. LCR, VF, ALC collected data. All authors read and approved the final manuscript.

## REFERENCES


1. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers. 2015 25;1:15015.

2. Garrigue S, Pépin J-L, Defaye P, Murgatroyd F, Poezevara Y, Clémenty J, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. Circulation. 2007 Apr 3;115(13):1703–9.

3. Defaye P, Pépin J-L, Poezevara Y, Mabo P, Murgatroyd F, Lévy P, et al. Automatic recognition of abnormal respiratory events during sleep by a pacemaker transthoracic impedance sensor. J Cardiovasc Electrophysiol. 2004 Sep;15(9):1034–40.

4. Defaye P, de la Cruz I, Martí-Almor J, Villuendas R, Bru P, Sénéchal J, et al. A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. Heart Rhythm. 2014 May;11(5):842–8.

5. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart J. 2014 Oct 21;35(40):2797–815.

6. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200–7.

7. Champ-Rigot L, Ferchaud V, Prévost J-N, Moirot P, Pellissier A, Legallois D, et al. Rationale and Design for a Monocentric Prospective Study: Sleep Apnea Diagnosis Using a Novel Pacemaker Algorithm and Link With Aldosterone Plasma Level in Patients Presenting With Diastolic Dysfunction (SAPAAD Study). Clin Med Insights Cardiol. 2018;12:1179546817751628.

8. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013 Aug;15(8):1070–118.

9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321–60.

10. Aimé E, Rovida M, Contardi D, Ricci C, Gaeta M, Innocenti E, et al. Long-term screening for sleep apnoea in paced patients: preliminary assessment of a novel patient management flowchart by using automatic pacemaker indexes and sleep lab polygraphy. Heart Lung Circ. 2014 Oct;23(10):943–50.

11. Dias M, Gonçalves I, Amann B, Marques P, Martinho C, Leitão C, et al. Utility of new-generation pacemakers in sleep apnea screening. Sleep Med. 2017 Sep;37:27–31.

12. Chen R, Chen K, Dai Y, Zhang S. Utility of transthoracic impedance and novel algorithm for sleep apnea screening in pacemaker patient. Sleep Breath. 2019 Sep;23(3):741–6.

13. Padeletti M, Vignini S, Ricciardi G, Pieragnoli P, Zacà V, Emdin M, et al. Sleep disordered breathing and arrhythmia burden in pacemaker recipients. Pacing Clin Electrophysiol. 2010 Dec;33(12):1462–6.

14. El Shayeb M, Topfer L-A, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. CMAJ. 2014 Jan 7;186(1):E25-51.

15. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007 Dec 15;3(7):737–47.

16. Escourrou P, Meslier N, Raffestin B, Clavel R, Gomes J, Hazouard E, et al. [Which clinical approach and which diagnostic procedures for obstructive sleep apnea syndrome?]. Rev Mal Respir. 2010 Oct;27 Suppl 3:S115-123.

17. Moubarak G, Bouzeman A, de Geyer d'Orth T, Bouleti C, Beuzelin C, Cazeau S. Variability in obstructive sleep apnea: Analysis of pacemaker-detected respiratory disturbances. Heart Rhythm. 2017 Mar;14(3):359–64.

18. Bodez D, Damy T, Soulat-Dufour L, Meuleman C, Cohen A. Consequences of obstructive sleep apnoea syndrome on left ventricular geometry and diastolic function. Arch Cardiovasc Dis. 2016 Sep;109(8–9):494–503.

19. Arias MA, García-Río F, Alonso-Fernández A, Mediano O, Martínez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005 Jul 19;112(3):375–83.

20. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009 Jun;11(6):602–8.

21. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003 Jan 8;289(2):194–202.

22. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. Chest. 2007 Feb;131(2):453–9.

23. Gonzaga CC, Gaddam KK, Ahmed MI, Pimenta E, Thomas SJ, Harding SM, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. J Clin Sleep Med. 2010 Aug 15;6(4):363–8.

24. de Souza F, Muxfeldt ES, Margallo V, Cortez AF, Cavalcanti AH, Salles GF. Effects of continuous positive airway pressure treatment on aldosterone excretion in patients with obstructive sleep apnoea and resistant hypertension: a randomized controlled trial. J Hypertens. 2017 Apr;35(4):837–44.

25. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. Eur Heart J. 2008 Jul;29(13):1662–9.

26. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015 May;169(5):647-654.e2.

27. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013 Jul 23;62(4):300–5.

28. Marti-Almor J, Marques P, Jesel L, Garcia R, Di Girolamo E, Locati F, et al. Incidence of sleep apnea and association with atrial fibrillation in an unselected pacemaker population: Results from the observational RESPIRE study. Heart Rhythm. 2019 Sep 4;

## 2ème partie : La méthode de mesure de la fraction d'éjection du ventricule gauche a-t-elle un impact sur la prédiction des évènements cliniques au décours de l'implantation d'un défibrillateur prophylactique ?

Le but de cette étude était d'évaluer si la FEVG, mesurée par imagerie par résonnance magnétique (FEVG-IRM) ou par échocardiographie bidimensionnelle (FEVG-2D), pouvait prédire différemment la survenue d'évènements cliniques chez les patients ayant bénéficié de l'implantation d'un défibrillateur en prévention primaire de MS.

Cette étude rétrospective a donc inclus, parmi les patients ayant eu la pose d'un défibrillateur en prévention primaire au CHU de Caen entre 2005 et 2014, ceux qui ont eu à la fois une échocardiographie et une IRM cardiaque au cours des trois mois précédant l'implantation. Le critère de jugement principal, combiné, associait la survenue d'un décès ou de thérapies appropriées délivrées par le défibrillateur au cours du suivi.

En raison d'un nombre assez faible de patients ayant eu accès à l'IRM en pré-implantation, seuls 173 patients sur les 534 ayant eu un DAI en prévention primaire ont été inclus. Parmi eux, 120 avaient une cardiomyopathie ischémique et 53 une cardiomyopathie dilatée. Nous avons tout d'abord mis en évidence une faible concordance entre les mesures de FEVG par les deux modalités d'imagerie. La FEVG-IRM moyenne était significativement plus basse que la FEVG-2D (24%±6 versus 28%±6, p<0,001).

Au cours du suivi (moyenne 50,3 mois+/-30,3), 66 patients sont décédés ou ont reçu au moins une thérapie appropriée. La FEVG-IRM était significativement inférieure chez les patients ayant présenté le critère primaire par rapport aux autres (22% vs 24%, p<0,01), alors que la FEVG-2D ne différait pas selon la survenue du critère primaire. Par la méthode ROC, des valeurs seuils de FEVG ont été déterminées pour chacune des modalités d'imagerie. Le seuil de FEVG-IRM à 22% était associé à un Hazard Ratio (HR) de 2,22 pour la survenue décès ou

thérapie appropriée (IC 95% 1,34 à 3,69 ; p=0,002), alors que le seuil de FEVG-2D n'était pas significativement associé à la survenue du critère primaire (HR=1,61 ; IC 95% 0,99 à 2,61 ; p=0,056). La présence de fibrose myocardique se traduisant par un rehaussement tardif (RT) à l'IRM était également prédictive de la survenue du critère primaire, et la combinaison de la FEVG-IRM <22% et du RT améliorait la prédiction d'évènements par rapport à chaque élément pris séparément (HR=2,58 ; IC 95% 1,54 à 4,3 ; p<0,001).

La mortalité toute cause était plus importante chez les patients ayant une FEVG-IRM <22% comparés aux patients avec une FEVG ≥22% (p=0,026) alors que la FEVG-2D n'était pas différente chez les patients décédés comparés aux survivants.

Nous en avons conclu que la FEVG-IRM permettait de mieux prédire la survenue d'évènements cliniques chez les patients implantés d'un DAI prophylactique et que l'association de cette mesure avec la présence d'un RT améliorait cette valeur prédictive. Ces données nous encouragent donc à recourir à la multimodalité pour l'évaluation des patients candidats à un DAI en prévention primaire.

**Article :**

**Champ-Rigot L**, Gay P, Benouda L, Morello R, Pellissier A, Alexandre J, Saloux E, Milliez P.

*Clinical outcomes after primary prevention defibrillator implantation are better predicted when left ventricular ejection fraction is assessed by magnetic resonance imaging.*

**Clinical outcomes after primary prevention defibrillator implantation are better predicted when the left ventricular ejection fraction is assessed by magnetic resonance imaging**

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## ABSTRACT

**Background:** The left ventricular ejection fraction (LVEF) is the key selection criterion for an implantable cardioverter defibrillator (ICD) in primary prevention of sudden cardiac death. LVEF is usually assessed by two-dimensional echocardiography, but cardiac magnetic resonance (CMR) imaging is increasingly used. The aim of our study was to evaluate whether LVEF assessment using CMR imaging (CMR-LVEF) or echocardiography (2D-LVEF) may predict differently the occurrence of clinical outcomes.

**Methods:** In this retrospective study, we reviewed patients referred for primary prevention ICD implantation to Caen University Hospital from 2005 to 2014. We included 173 patients with either ischemic (n=120) or dilated cardiomyopathy (n=53) and who had undergone preimplantation CMR imaging. The primary composite end point was the time to death from any cause or first appropriate device therapy.

**Results:** The mean CMR-LVEF was significantly lower than the mean 2D-LVEF (24%±6 vs 28%±6, respectively; p<0.001). CMR-LVEF was a better independent predictive factor for the occurrence of the primary composite endpoint with a cut-off value of 22% (Hazard Ratio [HR]=2.22; 95% CI [1.34-3.69]; p=0.002) than 2D-LVEF with a cut-off value of 26% (HR=1.61; 95% CI [0.99-2.61]; p=0.056). Combination of the presence of scar with CMR-LVEF<22% improved the predictive value for the occurrence of the primary outcome (HR=2.58; 95% CI [1.54-4.30]; p<0.001). The overall survival was higher among patients with CMR-LVEF≥22% than among patients with CMR-LVEF<22% (p=0.026), whereas 2D-LVEF was not associated with death.

**Conclusions:** CMR-LVEF is better associated with clinical outcomes than 2D-LVEF in primary prevention using an ICD. Scar identification further improved the outcome prediction. The combination of CMR imaging and echocardiography should be encouraged in addition to other risk markers to better select patients.

**KEY WORDS:** cardiac magnetic resonance imaging, echocardiography, left ventricular ejection fraction, late gadolinium enhancement, implantable cardioverter defibrillator, primary prevention

## BACKGROUND

Randomized controlled trials have proven the benefit of implantable cardioverter defibrillator (ICD) therapy in patients with altered left ventricular ejection fraction (LVEF) in both secondary and primary prevention of sudden cardiac death [1-7]. The only reliable criterion to select candidates for primary prevention ICD is the severity of LVEF impairment. Two-dimensional echocardiography (2DE) is widely used despite several limitations, particularly high intra and inter observer variability. Moreover, Simpson's biplane method is based on geometric assumptions inconsistent with wall deformations occurring in dilated failing ventricles; however, cardiac magnetic resonance (CMR) imaging is more accurate [8] and is considered the gold standard for LVEF assessment [9]. Nevertheless, current guidelines recommend ICD implantation for patients with LVEF <35% regardless of the imaging method [10, 11]. Late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) imaging also allows scar identification known as the malignant arrhythmia substrate [12].

The aim of our study was to evaluate whether LVEF assessment with either CMR imaging (CMR-LVEF) or echocardiography (2D-LVEF) may predict differently the occurrence of clinical outcomes among patients referred for primary prevention ICD implantation.

## METHODS

In this study, we retrospectively assessed patients referred to Caen University Hospital for primary prevention ICD implantation from January 2005 to December 2014. We included patients who had undergone both 2DE and CMR imaging less than three months prior to implantation. All the patients met the implantation criteria according to the guidelines currently used during the inclusion period [13, 14]: patients with ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM) in New York Heart Association (NYHA) class II or III and LVEF ≤35%; before the updated guidelines in 2008, patients with ICM and LVEF <30% regardless of NYHA class. They were all stable and under optimal medical therapy. The exclusion criteria were as follows: ICD implantation for another structural heart disease (i.e.,

hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, infiltrative cardiomyopathy or inherited primary arrhythmia syndromes); extended delay (>90 days) between 2DE and CMR; a significant clinical event (i.e., hospitalization, atrial fibrillation, and cardiac rehabilitation) between each LVEF assessment or before implantation; poor 2DE imaging quality with nonreliable LVEF assessment. In the case of LVEF mismatch, defined as LVEF ≤35% with one imaging modality but >35% with the other, ICD implantation was decided after team consensus. Demographic data and clinical features from the patients enrolled were anonymously collected from medical records.

**Echocardiography**

Echocardiograms were acquired by two experienced sonographers using either SONOS 5500® (Philips Healthcare, Amsterdam, Netherlands) or IE33® (Philips Healthcare, Amsterdam, Netherlands) with a 3.5-MHz probe. Three cardiac cycles were recorded in sinus rhythm and ten in the case of atrial fibrillation. In the case of poor image quality, ultrasound contrast agent (Sonovue®; Bracco International BV, Amsterdam. Netherlands) was injected. The data were reviewed and analyzed offline using commercially available software (Xcelera®; Philips Healthcare, Amsterdam, Netherlands) by two investigators blinded to any clinical or imaging data. 2D-LVEF was computed from the left ventricular end-diastolic volume and end-systolic volume using the biplane Simpson's method on two- and four-chamber apical views. The endocardial border was manually delineated according to the American Society of Echocardiographic recommendations [15].

**CMR studies and analysis**

CMR imaging was performed on a 1.5 Tesla CMR scanner (Signa Excite MR 1.5T; GE Healthcare, Chicago, IL, United States), with a 5-element phased-array body coil. Electrocardiographically gated localizing sequences were used to identify the long axis of the

heart to allow imaging of the left ventricle in the anatomically correct short-axis plane. Cine images were acquired for 10- to 15-second breath-holds with a temporal resolution of 25 frames/cardiac cycle. In all patients, a stack of steady-state free precession gradient-echo cine images were acquired in short axis. The slice thickness was 8 mm with no gap from the mitral annulus to the apex to fully cover the left ventricle. Contrast-enhanced images were acquired approximately 15 minutes after a bolus injection of gadoterate meglumine, Dotarem™ 0.15 mmol/kg (Guerbet, Aulnay-sous-Bois, France) using a standard two-dimensional inversion recovery gradient-echo sequence. In the case of atrial fibrillation, a mean representative cycle was selected. All analyses were performed by an experienced cardiologist blinded to any clinical or imaging data using the freely available validated cardiovascular image analysis software package Segmentv1.9 (http://segment.heiberg.se) [16]. Short-axis cine images were used to determine the end-diastolic volume, end-systolic volume, and LVEF. Papillary muscles were regarded as part of the ventricular cavity. Scar analysis was performed using short-axis LGE-CMR images. Endocardial and epicardial left ventricular borders as scar tissue were semiautomatically delineated in each LV short-axis slice and then were manually corrected. We worked using a binary approach to characterize scar tissue (normal myocardium vs. scar tissue).

**ICD implantation**

All the patients were implanted according to the standard surgical technique. Patients who met the required criteria (NYHA class ≥2 associated with left-bundle branch block QRS morphology and QRS duration>120-130 ms or non-left bundle branch block QRS morphology and QRS duration >150 ms) were implanted with a cardiac resynchronization therapy defibrillator. All manufacturers were represented in our population: Saint Jude Medical (Saint Paul, Minnesota, USA), Medtronic (Minneapolis, Minnesota, USA), Biotronik (Berlin, Germany), Boston Scientific (Malborough, Massachusetts, USA), and Sorin Group (Clamart, France). The devices were programmed using two or three zones: an optional monitoring zone without

therapy, a ventricular tachycardia zone (>170/min) with anti-tachycardia pacing followed by shocks and a ventricular fibrillation (>214/min) zone with shocks.

**Clinical follow up and end points**

Patient follow up was conducted according to our standard of care with clinical examination and device interrogation. It was performed before hospital discharge, at one month and every six months. The patients were given a remote monitoring system, if available, and were followed as other patients every six months. Appropriate device therapy (ADT) was defined as an episode of anti-tachycardia pacing and/or internal shocks delivered to terminate ventricular arrhythmia as previously defined. All ADTs were confirmed by a specialized electrophysiologist who analyzed device reports and electrograms. Inappropriate therapies were defined as anti-tachycardia pacing and/or internal shocks delivered in the case of supraventricular tachycardia, T-wave detection, noise (i.e., electromyogram) or lead failure. The primary end point was defined as the occurrence of the first composite event including death or ADT. Secondary end points were all-cause mortality and the occurrence of the first ADT.

**Statistical analysis**

Continuous variables were expressed as the means ± standard deviation (SD) if normally distributed and as medians and interquartile range if not normally distributed. Categorical variables were expressed as numbers and percentages. Continuous data were compared using Student's *t*-test or the Mann-Whitney test as appropriate. Comparisons between categorical or dichotomous data were performed using chi-square test or Fisher's exact test depending on validity criteria. Reproducibility between the imaging techniques was performed using Bland and Altman analysis. Survival time until the first ADT or death was defined as the number of days between implantation to the first event. If a patient did not experience any end point during the follow-up period, the outcome was considered censored. Univariate and

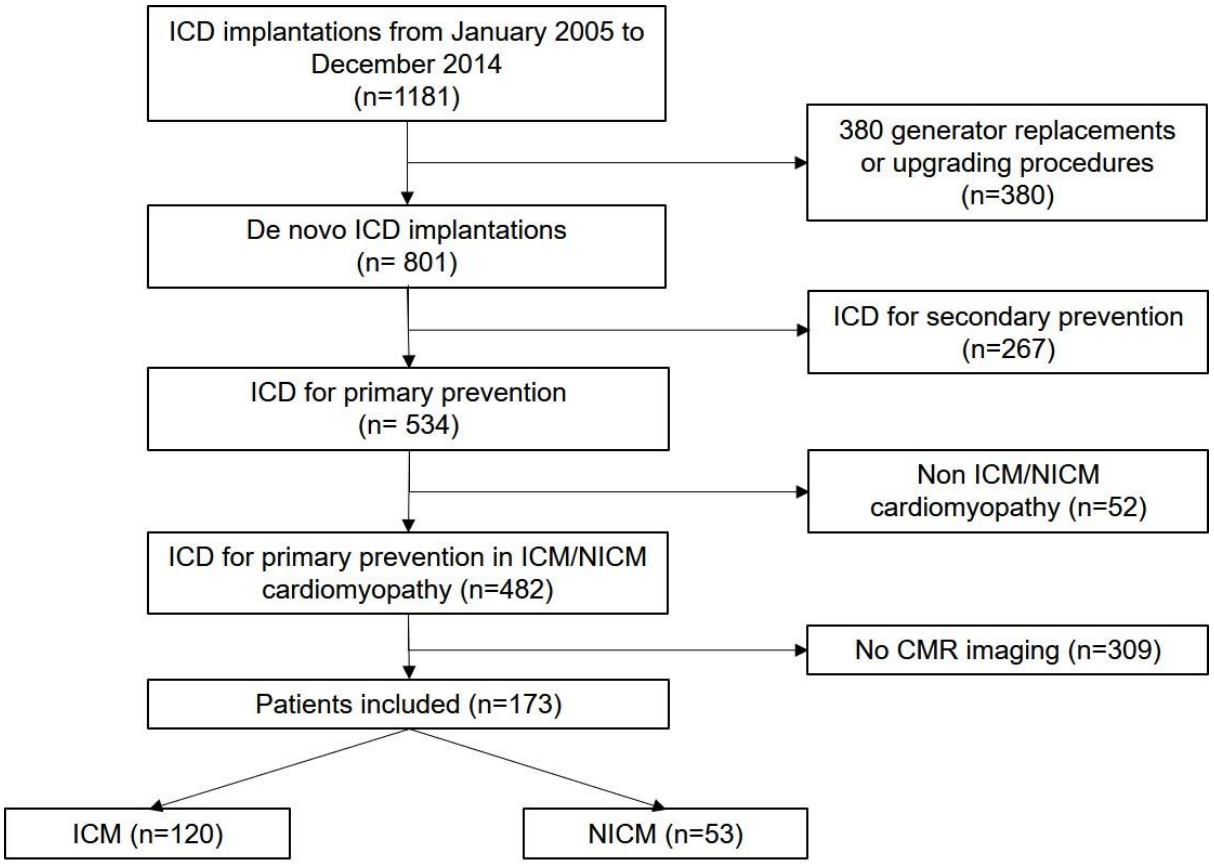
multivariate Cox regression analyses were used to examine the association between the baseline characteristics and occurrence of the first ADT or all-cause mortality. Each variable with a p value <0.15 in univariate analysis was introduced in multivariate analysis. The assessment of 2D-LVEF and CMR-LVEF threshold values to predict the occurrence of ADT or mortality was realized using the receiver operating characteristic (ROC) curve method. Survival analysis and comparisons between subgroups defined using LVEF thresholds were evaluated using Kaplan-Meier estimates and the log-rank test. All statistical analyses were performed using IBM SPSS Statistics, version 20.0 (released 2011; IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

## RESULTS

During the study period, 1,181 patients were successfully implanted with an ICD at Caen University Hospital, including 534 with ICM or NICM referred for primary prevention of sudden cardiac death. One hundred seventy-three of them underwent both preimplantation CMR imaging and 2DE; therefore, they were included in our study (Figure 1). The mean age was 59±12 years; the patients were mostly men (86%), with ICM in 69%. Most of them had mild dyspnea and were in NYHA II class. Medical therapy was optimized with 94% of patients receiving a beta-blocker, 94% receiving a renin-angiotensin system blocker and 61% receiving a mineralocorticoid receptor antagonist. The mean QRS duration was 124±34 milliseconds, and 32% of the patients received a resynchronization device. The baseline characteristics are all summarized in Table 1. During the mean follow up of 50±30 months, death occurred in 46 patients (26.6%). We observed ADT in 30 patients (17.3%) and seven inappropriate therapies (4%).

**Figure 1. Study flow chart**

CMR: cardiac magnetic resonance; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; NICM: nonischemic cardiomyopathy




**LVEF measurement with echocardiography and CMR imaging**

At the time of implantation, the mean CMR-LVEF (24±6%) was significantly lower than the mean 2D-LVEF (28±6%) ($p<0.001$). The intraclass correlation coefficient between 2D-LVEF and CMR-LVEF was 0.466 ($p<0.001$). Figure 2 represents the mean difference between 2D-LVEF and CMR-LVEF for each patient according to the Bland and Altman method. The overall mean difference between 2D-LVEF and CMR-LVEF was 4±7%. The limits of agreement were wide between the two methods (-9.5 to 17.3).

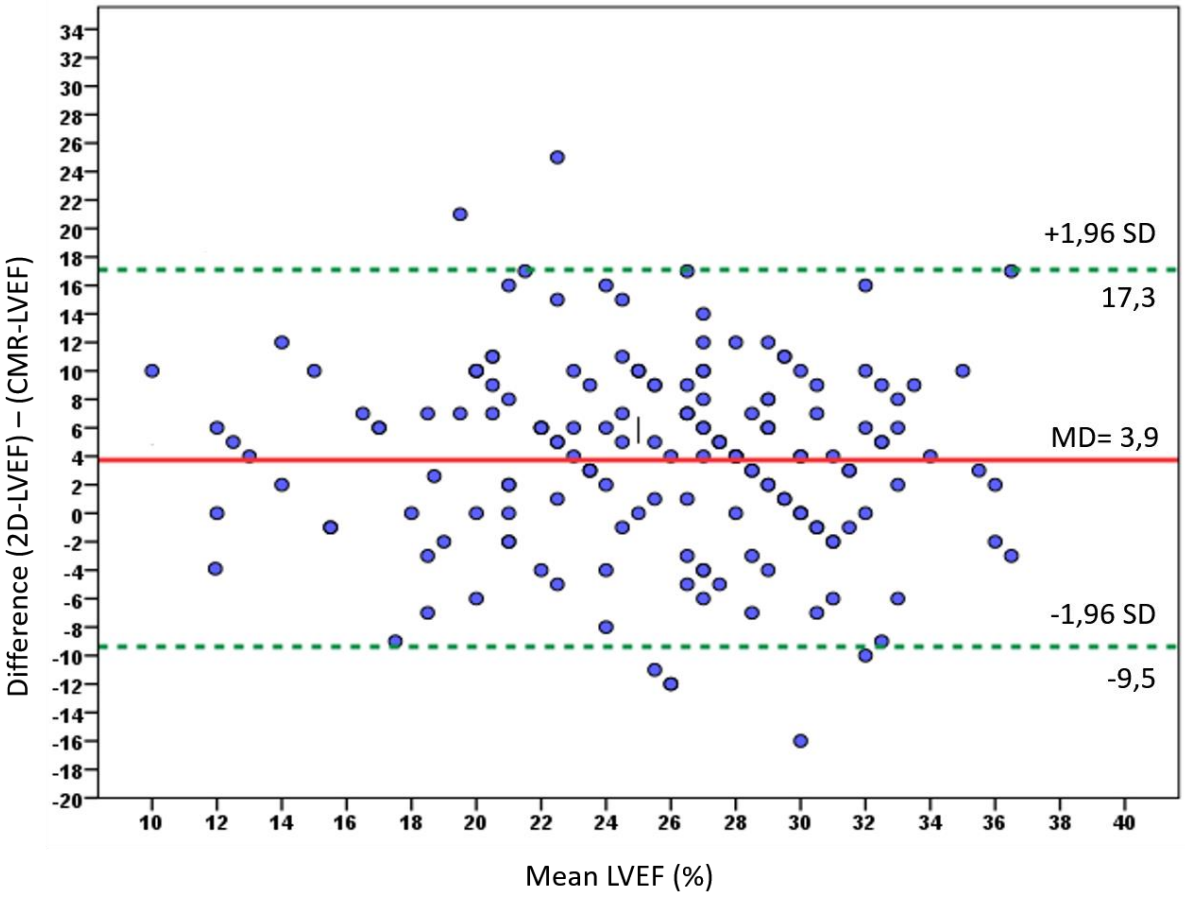
**Table 1. Characteristics of the patients at baseline and according to the primary end point occurrence**

Continuous variables are normally distributed, expressed as the means and standard deviation. AF: atrial fibrillation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; CMR-LVEF: left ventricular ejection fraction measured by cardiac magnetic resonance imaging; ICM: ischemic cardiomyopathy; LGE: late gadolinium enhancement; MRA: mineralocorticoid receptor antagonist; ms: millisecond; NYHA: New York Heart Association; ppm: pulse per minute; SD: standard deviation; 2D-LVEF: left ventricular ejection fraction measured by echocardiography

| | N=173 | Death or ADT | | p | p for survival |
|---|---|---|---|---|---|
| | | Yes (n=66) | No (n=107) | | |
| **Follow-up, months (mean±SD)** | 50.3 ± 30.3 | 52.5 ± 28.7 | 46.7 ± 32.7 | 0.223 | |
| **Age, years (mean±SD)** | 59 ± 12 | 60 ± 13 | 58 ±11 | 0.554 | ≥58 vs < 58 : 0.979 |
| **Male, n (%)** | 149 (86) | 62 (94) | 87 (81) | 0.023 | 0.206 |
| **ICM, n (%)** | 120 (69) | 54 (82) | 66 (62) | 0.006 | 0.046 |
| **Diabetes mellitus, n (%)** | 40 (23) | 14 (21) | 26 (24) | 0.712 | 0.819 |
| **Hypertension, n (%)** | 49 (28) | 24 (36) | 25 (23) | 0.082 | 0.046 |
| **Smokers, n (%)** | 64 (37) | 28 (42) | 36 (34) | 0.260 | 0.918 |
| **AF, n (%)** | 35 (20) | 20 (30) | 15 (14) | 0.012 | 0.196 |
| **NYHA class, n (%)**<br>I<br>II<br>III | <br>28 (16)<br>99 (57)<br>46 (27) | <br>9 (14)<br>35 (53)<br>22 (33) | <br>19 (18)<br>64 (60)<br>24 (22) | 0.270 | II vs I: 0.508<br>III vs I: 0.079<br>III vs I+II: 0.054 |
| **Heart rate, ppm (mean±SD)** | 69 ± 16 | 66 ± 13 | 71 ± 18 | 0.108 | 0.354 |
| **QRS duration, ms (mean±SD)** | 124 ± 33 | 121 ± 32 | 125 ± 34 | 0.413 | 0.384 |
| **Creatinine level, µmol/L (mean±SD)**<br>**Creatinine level ≥110 µmol/L, n (%)** | 107 ± 36<br>65 (38) | 117 ± 41<br>34 (52) | 100 ± 30<br>31 (29) | 0.002<br>0.003 | 0.005<br>0.007 |
| **Betablockers, n (%)** | 163 (94) | 64 (97) | 99 (93) | 0.321 | 0.270 |
| **ARB or ACEI, n (%)** | 163 (94) | 62 (94) | 101 (94) | 1.000 | 0.661 |
| **Diuretics, n (%)** | 124 (72) | 47 (71) | 77 (72) | 1.000 | 0.939 |
| **MRA, n (%)** | 105 (61) | 41 (62) | 64 (60) | 0.873 | 0.556 |
| **Resynchronization therapy, n (%)** | 56 (32) | 21 (32) | 35 (33) | 1.000 | 0.978 |
| **Complications, n (%)** | 23 (13) | 9 (14) | 14 (13) | 1.000 | 0.627 |
| **2D-LVEF, % (mean±SD)**<br>**2D-LVEF<26, n (%)** | 27.5 ±6.3<br>63 (36) | 27 ± 6<br>30 (46) | 28 ± 7<br>33 (33) | 0.500<br>0.141 | 0.256<br>0.052 |
| **CMR-LVEF, % (mean±SD)**<br>**CMR-LVEF<22, n (%)** | 23.4 ± 6.7<br>60 (35) | 22 ± 7<br>28 (42) | 24 ± 7<br>32 (30) | 0.087<br>0.102 | 0.010<br>0.005 |
| **LGE, n(%)** | 133 (77) | 58 (87) | 75 (71) | 0.017 | 0.058 |
| **LGE and CMR-LVEF<22, n(%)** | 44 (25) | 26 (39) | 18 (18) | 0.002 | <0.001 |

**Figure 2. Bland and Altman plots of differences in the 2D-LVEF and CMR-LVEF**

The red line represents the mean paired difference, and the green dotted lines represent the 95% limits of agreement. LVEF: left ventricular ejection fraction; 2D-LVEF: LVEF measured by two-dimensional echocardiography; CMR-LVEF: LVEF measured by cardiac magnetic resonance imaging; MD: mean difference; SD: standard deviation.




**Occurrence of death or appropriate device therapy**

The primary end point, death from any cause or the first ADT, occurred in 66 patients (38%). During the follow up, 10 patients received ADT before death and were censored for primary end point analysis. There was no difference between patients who met the primary end point regarding age, sex ratio or treatment. There was a trend toward a higher risk of meeting the primary end point for patients in NYHA class III than for patients in NYHA class I or II (p=0.054). ICM was significantly associated with death or ADT (81.8% vs 61.7%, p= 0.006) and correlated with survival (p=0.046). A higher creatinine level was also found to be associated with the

occurrence of death or ADT (p=0.005). The characteristics of patients according to the occurrence of the primary end point are summarized in Table 1.

- *Primary endpoint prediction using 2D-LVEF and CMR-LVEF*

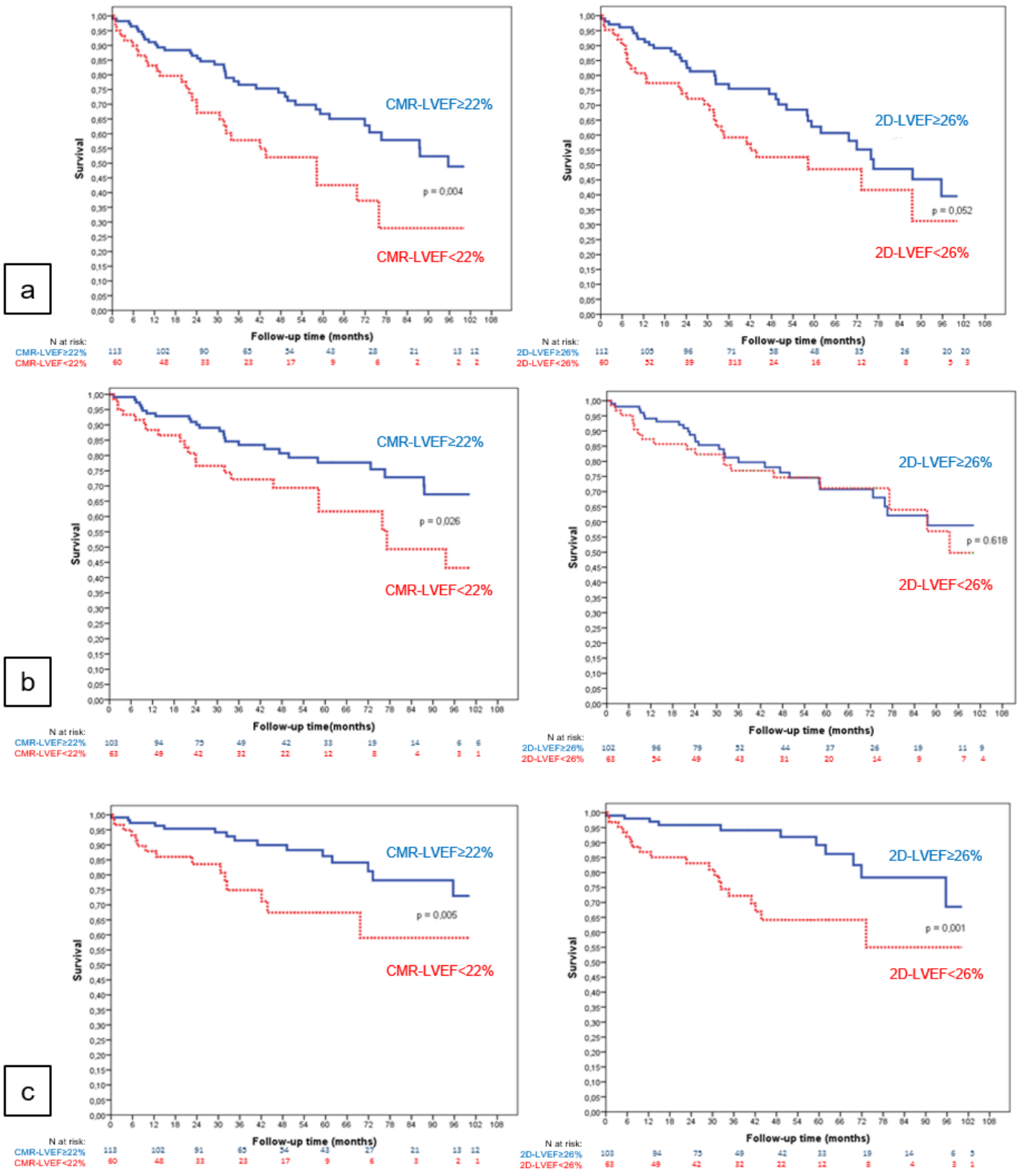
Patients who died or received ADT had lower CMR-LVEF (22±7%) than those who did not (24±7%) (p=0.01), whereas the mean 2D-LVEF was not different between those patients. We identified LVEF threshold values to stratify patients with a higher risk of death or ADT by ROC curve analysis. Event-free survival was greater among the patients with CMR-LVEF≥22% (p=0.04). After Cox regression, we found that CMR-LVEF<22% was associated with a 2.22 greater risk of death or ADT during follow-up (95% CI [1.34-3.69]; p=0.002). There was a trend toward better survival among patients with 2D-LVEF≥26% (p=0.052), and 2D-LVEF<26% was associated with a 1.61 higher risk of meeting the primary end point (95% CI [0.99-2.61]; p=0.056) (Figure 3, panel a). Among the 120 patients with ICM, the mean CMR-LVEF was significantly lower in the case of death or ADT (22% versus 25%, p=0.027). There was also a trend toward a lower 2D-LVEF when the primary end point occurred (27% versus 29%, p=0.088). Conversely, neither CMR nor 2D-LVEF was associated with the primary end point occurrence in patients with NICM.

- *Scar identification combined with LVEF*

In our study population, we found LGE in 133 patients of 173 (76.9%). LGE presence was significantly associated with the primary outcome occurrence (p=0.017) with a trend toward an impact on survival without death or ADT (p=0.058 for the log-rank test). We combined LGE and LVEF thresholds as previously described and found improvement in the outcome prediction. Survival free from the primary outcome was significantly lower in patients with CMR-LVEF<22% and LGE with a 2.58 HR (95% CI [1.54-4.30]; p<0.001).

**Figure 3. Survival curves based on left ventricular ejection fraction assessed by cardiac magnetic resonance imaging (CMR-LVEF) or echocardiography (2D-LVEF)**

a: Primary composite end point of death or appropriate device therapy; b: Death; c: Appropriate device therapy.



**Mortality**

At the end of the follow up, 46 patients died (26.6%). NYHA class III (p=0.002), atrial fibrillation (p=0.02) and a high level of plasmatic creatinine (p=0.001) were associated with the risk of death in our study. The overall survival was higher among patients with CMR-LVEF≥22% than among patients with CMR-LVEF<22% (p=0.026). CMR-LVEF<22% was associated with the risk of death in both univariate and multivariate analyses with a 2.02 HR (95% CI [1.1-3.69]; p=0.02). By contrast, the mean 2D-LVEF was not different in patients who died compared with the others and the previous 2D-LVEF threshold was not associated with the overall survival (Figure 3, panel b).

**Appropriate device therapy**

During the follow up, 30 patients (17%) experienced ADT. We found no clinical characteristic predictive of ADT occurrence Conversely, survival free from ADT was significantly higher for patients with CMR-LVEF≥22% (p=0.005) or 2D-LVEF≥26% (p=0.001) (Figure 3, panel c).

**CMR and 2DE mismatch**

Among the patients, 17 had discordant LVEF measurements between CMR imaging and 2DE. Eleven had CMR-LVEF≤35% but 2D-LVEF>35% and would have not received an ICD in the case of echocardiography-based screening. Two of them died, and three experienced ADT. Conversely, six patients had 2D-LVEF≤35% but CMR-LVEF>35%; two of these died, and none had ADT. No difference was found in the outcomes irrespective of the type of LVEF mismatch. Moreover, survival was similar in patients with LVEF mismatch compared to the rest of the population.

## DISCUSSION

Our report, studying patients implanted with ICD for primary prevention according to the current guidelines, showed the following: CMR imaging and 2DE exhibited only moderate agreement to assess LVEF and 2D-LVEF was found to be higher than CMR-LVEF; CMR-LVEF was better associated with death or ADT than 2D-LVEF despite close threshold values; LGE presence improved the predictive value of CMR-LVEF.

### Discrepancies between 2D-LVEF and CMR-LVEF

Several reports have shown that CMR imaging was superior to 2DE and more reproducible for LVEF assessment [17]. Bellenger et al. [8] suggested in a direct comparison between these two modalities and radionuclide ventriculography that CMR imaging should be preferred regarding its three-dimensional approach and high image quality. Particularly, at lower LVEF, 2DE generally overestimates LVEF compared with CMR imaging [8, 18, 19]. We found a systematic bias of 4±7% between 2D-LVEF and CMR-LVEF. Higher LVEF measurements by 2DE compared with CMR was already pointed out by Rijnierse et al. [20] who found a mean difference of 6±7%. In daily practice, a five-percent difference in LVEF could be considered non relevant. However, because the guidelines are based on the 35% cut-off value, the choice of either 2D-LVEF or CMR-LVEF could result in the reclassification of patients for ICD eligibility. This issue affects patients with borderline LVEF. Indeed, having a 2D-LVEF within five percent of commonly used thresholds was found to be predictive of reclassification by CMR for ICD implantation [18].

### CMR-LVEF and cardiac events

Some reports have already shown that using the same threshold value with CMR imaging and 2DE would result in a greater number of patients to implant with CMR imaging [18-21]. In a retrospective study including patients selected for ICD according to CMR-LVEF≤35%, Rijnierse et al. [20] showed that 19% of patients would not have been implanted according to 2D-LVEF. These patients had a significantly lower rate of ADT than those with 2D-LVEF<35%

[20]. Conversely, Rayatzadeh et al. [21] found in their primary prevention population selected according to 2D-LVEF that 25% of the patients did not meet ICD eligibility based on CMR imaging. Those patients experienced no appropriate therapy [21]. Based on different data, they both suggested to use a different and lower cut-off value for CMR-LVEF to better assess ICD eligibility. To further explore this hypothesis, we did not compare the eligibility according to the imaging method but sought to analyze both 2D and CMR-LVEF correlation with cardiac events. Finally, we found that the LVEF cut-off values to predict death or ADT were very low, either with CMR imaging or 2DE and much lower than the recommended 35% cut-off. It is worth noting that the same comments were addressed to the large randomized trials that included patients with lower LVEF than the inclusion criteria requirements. The mean LVEF in those studies was 20 to 25% [1, 4, 5, 22], and the European guidelines committee already warned about inconsistencies in recommendations based on these results [13]. The average LVEF differences between patients with events (death or ADT) and others were low in our study (<5%). Nevertheless, one of the major findings of our work is that the CMR-LVEF threshold seemed better correlated with the clinical outcomes than 2D-LVEF in a real-life population of primary prevention patients. The overall survival was stratified by the CMR-LVEF threshold, whereas the 2D-LVEF cut-off value was only associated with the occurrence of ADT. Recently, the DANISH trial showed that prophylactic ICD implantation was not associated with better survival in nonischemic patients [23]. Our study population, especially the NICM group, was too small to draw any conclusion. However, Gao et al. [24] have already shown that patients with ICM who experienced ADT or survived cardiac arrest or sudden cardiac death had significantly lower CMR-LVEF than those without events, whereas LVEF was not different in cases of NICM. Although underpowered, our results are consistent with previous reports suggesting that LVEF alone might not be sufficient to select ICD candidates with NICM.

**Additional predictive value of LGE combined with CMR-LVEF**

Several studies have reported that LGE presence and extent were associated with ventricular arrhythmias in both ICM [25] and NICM [26]. A meta-analysis of 19 studies reported a pooled

odds ratio of 5.62 for ventricular arrhythmias in patients with LGE above study-defined thresholds with no difference between ICM and NICM subgroups [27]. Recently, a prospective study conducted in NICM patients reported a reduction in mortality with primary prevention ICD implantation only in patients presenting a left ventricular scar [28]. We showed that the combination of CMR-LVEF<22% and LGE presence improved the prediction of death or ADT in primary prevention patients with a 2.58 HR ($p<0.001$) over CMR-LVEF alone (HR=2.22; $p=0.002$).

**Possible clinical implications**

Currently, there is no other validated criterion to select patients for ICD-based primary prevention than LVEF. To better identify patients who will derive a benefit from ICD, there is growing evidence supporting CMR imaging use. Our study highlighted the CMR ability to identify patients with a higher risk of death or ventricular arrhythmias. CMR-LVEF alone was better associated with cardiac outcomes than 2D-LVEF, and the combination with myocardial scar presence further improved its predictive value. When available, CMR imaging can be useful in addition to echocardiography, especially for challenging situations—i.e., patients with borderline LVEF or NICM. Future studies will be needed to find a dedicated CMR-LVEF threshold, probably lower than 35%, to select patients and develop a risk model that should integrate CMR data (LVEF, LGE) and clinical features like NYHA class.

**Limitations**

This study was single-center and retrospective with a small sample size, especially the NICM subgroup, limiting definitive conclusions. CMR imaging prior to implantation occurred at the physician's discretion. At our center, as in other tertiary centers, access to this imaging modality is not easy to organize, especially for patients referred from other centers in our area. Numerous patients referred for primary prevention at our center were not evaluated with CMR imaging. We examined those patients regarding baseline characteristics age, gender, risk factors, type of cardiomyopathy, NYHA status, medications and LVEF prior to implantation

(see supplemental table). There was no difference in LVEF, QRS duration, the sinus rhythm rate, and the creatinine level. Nevertheless, patients with no CMR imaging were older, more symptomatic, had more hypertension, NICM, and received more CRT device. This last difference is likely to explain previous ones. This selection bias may limit our results interpretation because outcomes might have been different while considering patients with more severe conditions. We also did not retrieve sufficient three-dimensional echocardiography data to compare with 2DE and CMR imaging. 2DE and CMR imaging were not realized at the same time, and we could assume that LVEF modification might occur. However, there fewer than three months between them and patients experiencing a cardiac event during this period were excluded. Despite a possible important clinical implication, the "mismatch group" was far too small to support any conclusion about the outcomes of patients who have discordant LVEF measurements.

## CONCLUSION

In our population of patients selected for primary prevention ICD implantation, CMR-LVEF and 2D-LVEF showed poor agreement and CMR-LVEF was significantly lower. We found that CMR-LVEF was better associated with the risk of death and ADT than 2DE-LVEF. Furthermore, LGE detection associated with a low CMR-LVEF improved cardiac outcome prediction. Routine use of CMR imaging in addition to echocardiography should be supported in patients' evaluation for ICD in primary prevention.

## LIST OF ABBREVIATIONS

ADT: Appropriate device therapy

CMR: Cardiac magnetic resonance

CMR-LVEF: Left ventricular ejection fraction measured with cardiac magnetic resonance imaging

ICD: Implantable cardioverter defibrillator

ICM: Ischemic cardiomyopathy

LGE: Late gadolinium enhancement

LVEF: Left ventricular ejection fraction

NICM: Nonischemic cardiomyopathy

NYHA: New York Heart Association

ROC: Receiver operating characteristic

2DE: Two-dimensional transthoracic echocardiography

2D-LVEF: Left ventricular ejection fraction measured by two-dimensional transthoracic echocardiography

## DECLARATIONS

### Ethics approval and consent to participate

This retrospective study based on previous collected data complied with the Declaration of Helsinki and French ethics guidelines. This study was approved by the regional ethics committee and the French committee of informatics and civil liberties (CNIL, conformity agreement n°2204611). All patients provided written informed consent for intervention and received a non-opposition letter, as requested by French authorities for retrospective studies.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests in relation to the present work.

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**Authors' contributions**

LCR contributed to the study design, data collection, analysis and interpretation, and manuscript preparation. PG and LB contributed to the study design, data collection, analysis and interpretation and manuscript review. RM contributed to the study design, data analysis and interpretation, statistics, and manuscript review. AP, JA and ES contributed to the study design, echocardiography and CMR analyses, data analysis and interpretation and manuscript review. PM contributed to the study design, data analysis and interpretation and manuscript preparation. All the authors approved the final version of the submitted manuscript.

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Not Applicable

**Supplemental table 1**: **Characteristics of patients referred for CMR compared to controls**

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; CMR: cardiac magnetic resonance imaging; CRT: cardiac resynchronization therapy; ICM: ischemic cardiomyopathy; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NICM: nonischemic cardiomyopathy; NYHA: New York Heart Association

| | **total n=482** | **CMR n=173** | **No CMR n=309** | **p** |
|---|---|---|---|---|
| **Age** | | 59 (±12) | 65 (±10) | <0,001 |
| **male gender** | 407 (84,4) | 149 (86,1) | 258 (83,5) | 0,513 |
| **Hypertension** | 186 (39,9) | 49 (28,3) | 137 (46,8) | <0,001 |
| **Diabetes mellitus** | 119 (25,5) | 40 (23,1) | 79 (26,9) | 0,382 |
| **Creatinine level** | | 108 (±36,0) | 113,7 (±85,3) | 0,419 |
| **LVEF** | | 27,5 (±6,3) | 27,2 (±4,8) | 0,655 |
| **Sinus rhythm** | 399 (83) | 138 (79,8) | 261 (84,7) | 0,104 |
| **QRS duration** | | 123 (±33) | 127 (±34) | 0,289 |
| **NYHA** | | | | |
| 1 | 57 (11,8) | 28 (16,2) | 29 (9,4) | 0,006 |
| 2 | 258 (53,5) | 99 (57,2) | 159 (51,5) | |
| 3 | 167 (34,6) | 46 (26,6) | 121 (39,2) | |
| **Cardiomyopathy** | | | | |
| ICM | 292 (60,6) | 120 (69,4) | 172 (55,7) | 0,004 |
| NICM | 190 (39,4) | 53 (30,6) | 137 (44,3) | |
| **Medications** | | | | |
| Beta-blockers | 457 (95) | 163 (94,2) | 294 (95,5) | 0,663 |
| ACEI/ARB | 455 (94,6) | 163 (94,2) | 292 (94,8) | 0,835 |
| MRA | 238 (49,7) | 105 (60,5) | 133 (43,5) | <0,001 |
| Loop diuretics | 367 (76,5) | 124 (71,7) | 243 (79,2) | 0,073 |
| CRT | 208 (43,2) | 56 (32,4) | 152 (49,2) | <0,001 |

## REFERENCES


1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med. 1996;335:1933-40.

2. Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, et al. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. Circulation. 2002;106:233-8.

3. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J. 2000;21:2071-8.

4. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-83.

5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. N Engl J Med. 2005;352:225-37.

6. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50.

7. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy. JAMA. 2004;292:2874-9.

8. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000;21:1387-96.

9. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787-847.

10. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace. 2015;17:1601-87.

11. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society. Heart Rhythm. 2018;15:e190-252.

12. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, et al. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. JACC. 2012;60:408-20.

13. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force and the european society of cardiology committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). J Am Coll Cardiol. 2006;48:e247-346.

14. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29:2388-442.

15. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr. 1989;2:358-67.

16. Heiberg E, Sjögren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of segment - freely available software for cardiovascular image analysis. BMC Med Imaging. 2010;10:1.

17. Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90:29-34.

18. Joshi SB, Connelly KA, Jimenez-Juan L, Hansen M, Kirpalani A, Dorian P, et al. Potential clinical impact of cardiovascular magnetic resonance assessment of ejection fraction on eligibility for cardioverter defibrillator implantation. J Cardiovasc Magn Reson. 2012;14:69.

19. de Haan S, de Boer K, Commandeur J, Beek AM, van Rossum AC, Allaart CP. Assessment of left ventricular ejection fraction in patients eligible for ICD therapy: discrepancy between cardiac magnetic resonance imaging and 2D echocardiography. Neth Heart J. 2014;22:449-55.

20. Rijnierse MT, van der Lingen A-LCJ, Weiland MTD, de Haan S, Nijveldt R, Beek AM, et al. Clinical impact of cardiac magnetic resonance imaging versus echocardiography-guided patient selection for primary prevention implantable cardioverter defibrillator therapy. Am J Cardiol. 2015;116:406-12.

21. Rayatzadeh H, Patel SJ, Hauser TH, Ngo LL, Shaw JL, Tan A, et al. Volumetric left ventricular ejection fraction is superior to 2-dimensional echocardiography for risk stratification of patients for primary prevention implantable cardioverter-defibrillator implantation. Am J Cardiol. 2013;111:1175-9.

22. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NAM, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350:2151-8.

23. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016;375:1221-30.

24. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, et al. Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator. Circulation. 2012;5:448-56.

25. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. JACC. 2005;45:1104-8.

26. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. Circulation. 2005;112:2821-5.

27. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, et al. Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and nonischemic LV dysfunction. JACC. 2016;9:1046-55.

28. Gutman SJ, Costello BT, Papapostolou S, Voskoboinik A, Iles L, Ja J, et al. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. Eur Heart J. 2018;40:542-50.

## 3ème partie : Les facteurs prédictifs de réponse à la resynchronisation cardiaque diffèrent-ils entre les patients de plus et moins de 75 ans ?

Cette étude a donc évalué l'impact de l'âge (≥ ou < à 75 ans) sur les facteurs prédictifs de réponse clinique à la RC. Cette étude rétrospective a inclus tous les patients ayant été implantés d'un dispositif de RC entre janvier 2013 et décembre 2016 au Centre Hospitalier Universitaire de Caen. Le critère de jugement principal était un critère d'efficacité de la RC associant la survie à un an sans hospitalisation pour un épisode d'IC et l'amélioration du stade NYHA d'au moins une classe.

Parmi les 243 patients inclus, 102 étaient âgés de 75 ans ou plus et 131 de moins de 75 ans. Les patients âgés présentaient plus de comorbidités, avec un stade NYHA plus élevé que dans le groupe <75 ans (p=0,01), et avaient majoritairement été implantés avec un PM-RC (respectivement 48% versus 13%). L'altération de la FEVG en échographie était comparable entre les deux groupes (médiane à 28%). L'efficacité de la RC ne différait pas entre les deux groupes : 50% des patients du groupe <75 ans et 47% patients du groupe ≥75 ans ont présenté le critère d'amélioration à un an (p=0,69). En analyse uni et multivariée, le stade NYHA ≥III était le seul facteur prédictif d'efficacité de la RC chez les patients de 75 ans et plus (OR=6,02; IC 95% 1,33 à 18,77, p=0,002). Ce rôle du stade NYHA n'était pas retrouvé dans le groupe de patients <75 ans, tandis que la présence d'une FA était négativement associée à la réponse à la RC dans le groupe <75 ans (OR=0,28; IC 95% 0,13 à 0,62, p=0.001). La mortalité à un an était de 14% sans différence entre les groupes.

En revanche, la RC de sauvetage et la présence d'une FA étaient des facteurs indépendants de mortalité dans les deux groupes. Des complications sont survenues chez 21% des patients <75ans et chez 15% des patients ≥75 ans sans différence significative entre les groupes (p=0,19). La pose d'un défibrillateur (p=0,003) et l'élargissement des QRS à plus de150 ms (p=0,02) étaient des facteurs prédictifs de complications dans la population globale. Il n'y avait

pas de différence concernant les thérapies délivrées chez les patients porteurs d'un défibrillateur (p=0,2).

Ainsi, nous avons montré dans cette étude que la RC était efficace chez les patients âgés de 75 ans et plus, notamment les plus symptomatiques, avec une survie sans hospitalisation associée à une amélioration fonctionnelle équivalente à celle des patients plus jeunes. En dépit d'un terrain plus fragile, les patients plus âgés ne sont pas plus à risque de complications liées à la procédure.

**Article :**

**Champ-Rigot L**, Cornille AL, Ollitrault P, Pellissier A., Chequel M, Legallois D, Milliez P.

*Predictors of clinical outcomes after cardiac resynchronization therapy in patients ≥75 Years.*

**Predictors of clinical outcomes after cardiac resynchronization therapy in patients ≥75 years**

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## ABSTRACT

**Background:** Cardiac resynchronization therapy (CRT) benefit has been proved in selected patients with heart failure and reduced ejection fraction. Older patients have been underrepresented in CRT trials. This study was conducted to determine whether predictive factors of cardiac resynchronization therapy outcomes may differ in patients older and younger than 75 years.

**Methods:** Consecutive patients who received CRT device between 2013 and 2016 in our center were retrospectively included. The primary endpoint was CRT effectiveness defined as combination of survival for one year with no heart failure hospitalization and improvement by one or more NYHA classes. Secondary endpoints were mortality, complications, and device therapies.

**Results:** Among the 243 patients included, 102 were ≥75 years. CRT effectiveness was observed in 70 patients (50%) <75 years and in 48 patients (47%) ≥75 years (p=0.69). NYHA class ≥III (OR=6.02; CI95% [1.33-18.77], p=0.002) was a predictive factor of CRT effectiveness only in ≥75 years group, while in <75 years group atrial fibrillation was independently negatively associated with primary endpoint (OR=0.28; CI95% [0.13-0.62], p=0.001). One-year mortality rate was 14% with no difference between age groups. Rescue CRT and atrial fibrillation were independent predictive factors for mortality in both age groups. Eighty-two complications occurred in 45 patients (19%) with no difference between groups. Defibrillator use and QRS duration were independent predictive factors for complications in both age groups. There was no difference considering device therapies.

**Conclusion:** At one-year, CRT response is not compromised by patient's age. In older patients, highly symptomatic individuals with NYHA class ≥III have better outcomes after CRT.

**KEY WORDS:** Resynchronization therapy; heart failure; aged; treatment outcome

## BACKGROUND

Cardiac resynchronization therapy (CRT) has become a standard therapy in patients with chronic heart failure (HF) related to reduced left ventricular ejection fraction (LVEF). Large clinical trials have demonstrated CRT benefits on symptoms, quality of life and morbi-mortality on top of optimal medical therapy. Current guidelines recommend CRT for selected patients regardless of age status[1] although older patients, defined as ≥65 years, and especially those ≥75 have been underrepresented in these studies[2]. Prevalence of HF is increasing with age, and the European Survey on CRT reported that median age of patients was 70 with 31% patients ≥75 years[3]. A few reports already highlighted feasibility and efficiency of CRT in older patients but little is known about predictors of response in this population[4–8].

We aimed to determine age-related predictive factors of clinical outcomes in older patients receiving CRT.

## METHODS

### Study population

We retrospectively included consecutive patients referred at Caen Normandy University Hospital for CRT device implantation between January 2013 and December 2016. CRT was implanted according to contemporary European guidelines[9]: New-York Heart Association (NYHA) functional class II to ambulatory IV, LVEF ≤ 35%, QRS duration ≥ 120ms and left-bundle branch block (LBBB) QRS morphology or QRS duration ≥ 150ms and non-LBBB QRS morphology, despite optimized medical treatment. After publication of latest guidelines in 2016[1], minimum QRS duration required was 130ms in case of LBBB QRS morphology. Patients with ventricular pacing indication and reduced LVEF as well as those with previous device upgraded to CRT pacemaker or CRT defibrillator were also included. We also considered patients implanted for rescue CRT, defined as CRT device implanted for amine-dependent end-stage HF. We excluded patients under 18 years or lost to follow-up. We defined

older patients as those who were ≥75 years at the time of implantation and then divided our population into two age groups: <75 and ≥75 years.

**Device therapy**

CRT device was implanted using standard techniques. In case of atrial fibrillation (AF), atrioventricular node ablation was performed if medical treatment failed to achieve heart rate control. The choice between defibrillator and pacemaker for primary prevention of sudden cardiac death, as well as baseline programming were at the discretion of the attending physician.

**Data collection**

Evaluation of candidates for CRT implantation, except in case of rescue-CRT, had to be performed within 3-months before the procedure, including 12-lead electrocardiogram and standard two-dimensional echocardiography performed with IE 33™ or Epic 5™ system (Philips Healthcare, Amsterdam, Netherlands) in our center with LVEF measured using Simpson's biplane method. Clinical, biological, electrocardiogram and echocardiographic data were anonymously collected.

**Follow-up and clinical endpoints**

Patients' follow-up was scheduled according to our standard of care with physical examination and device interrogation, before hospital discharge, at one-month, six-month and one-year. Remote monitoring system was proposed if appropriate.

The primary endpoint was CRT effectiveness, defined as a modified combined clinical score previously described[5]: survival for one year with no heart failure hospitalization and improvement by ≥ one NYHA classes. Secondary endpoints were all-cause mortality, complications, and occurrence of device therapies in patients with a defibrillator. Appropriate device therapy was defined as anti-tachycardia pacing and/or internal shocks delivered to

terminate sustained ventricular arrhythmia. Device therapy delivered in any other circumstance was considered inappropriate.

### Statistical analysis

Categorical variables were expressed as numbers and percentages and compared using the Pearson Chi square or Fisher's exact test depending on validity criteria. Continuous variables were expressed as mean and standard deviation if normally distributed or median and interquartile range. They were then compared using the student T-test or the Mann-Whitney Test. Association between baseline characteristics and the occurrence of clinical event was evaluated by univariate analysis. Variables with p value ≤0.20 in univariate analysis were then introduced in multivariate analysis using binary logistic regression model with Wald's step-by-step method. Survival time for primary endpoint was defined as the number of days between implantation and the first event. If a patient didn't experience any endpoint during the follow-up period, his outcome was considered censored. The Kaplan- Meier method was used to construct survival curves, with the log-rank test used for comparison among groups. Statistical significance was set at a two-tailed probability level of <0.05. All analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp. Released 2011. Armonk, NY: IBM Corp.).

## RESULTS

### Baseline characteristics

Two hundred and fifty patients underwent CRT implantation; among them, 7 were excluded because of missing follow-up data. Hence, our study population comprised the remaining 243 patients, of which 102 (42%) were ≥75 years. Baseline characteristics according to age groups are summarized in Table 1. Patients were predominantly men but there were more women in ≥75 years group (23%) than in <75 years group (13%) (p=0.04). Patients ≥75 years were more symptomatic according to NYHA class, had more chronic kidney disease (CKD, defined by

estimated glomerular filtration <60ml/min/1.73m²), and loop diuretics but less aldosterone antagonists. However, patients ≥75 years were less likely to have defibrillator than those <75 years (52% versus 87% respectively; p<0.001). Both groups had comparable LVEF impairment with a median LVEF of 28% (23.5-30), and mostly a LBBB QRS morphology (79%). There was no difference regarding proportion of upgraded device, CRT for rescue therapy and time procedure.

**Primary endpoint**

There was no difference in CRT effectiveness between age groups with 70 patients considered responders out of 141 (50%) in <75 years group compared to 48 patients out of 102 (47%) in ≥75 years group (p=0.69). Outcomes are detailed in Table 1. In univariate and multivariate analyzes, NYHA class ≥III before implantation was associated with CRT response in overall population (OR=3.30; 95% confidence interval (CI 95%) [1.70-6.51], p<0.001). NYHA class ≥III was strongly predictive of CRT effectiveness among older patients (OR=6.02; CI 95% [1.33-18.77], p=0.002). In <75 years group, there was a trend toward better CRT response in patients with previous NYHA class ≥III (p=0.07).

**Table 1: Baseline characteristics and outcomes**

Continuous variables are reported as median and interquartile range; categorical variables as numbers and percentages. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease (defined by estimated glomerular filtration <60ml/mn/1.73m²); CRT: cardiac resynchronization therapy; CRT-D: CRT with defibrillator; HF: Heart failure; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New-York Heart Association; NIVCD: non-specific intraventricular conduction delay; RBBB: right bundle branch block.

| | **<75 years (n=141)** | **≥75 years (n=102)** | **p** |
|---|---|---|---|
| **Age (years)** | 64 (10) | 79 (7) | <0.001 |
| **Male gender, n (%)** | 122 (87) | 78 (77) | 0.04 |
| **Ischemic cardiomyopathy, n (%)** | 71 (50) | 63 (62) | 0.08 |
| **Atrial fibrillation, n (%)** | 66 (47) | 56 (57) | 0.14 |

| | | | |
|---|---|---|---|
| **Diabetes mellitus, n (%)** | 44 (31) | 29 (29) | 0.71 |
| **CKD, n (%)** | 62 (49) | 68 (72) | 0.001 |
| **NYHA functional class, n (%)** | | | |
| I | 3 (2) | 1 (1) | 0.01 |
| II | 57 (40) | 22 (21) | |
| III | 52 (37) | 62 (61) | |
| IV ambulatory | 7 (5) | 7 (7) | |
| IV in hospital | 22 (16) | 10 (10) | |
| **Rescue CRT, n (%)** | 14 (10) | 8 (8) | 0.58 |
| **Beta blocker, n (%)** | 119 (85) | 78 (79) | 0.21 |
| **ACEI or ARB, n (%)** | 112 (80) | 71 (72) | 0.14 |
| **Aldosterone antagonist, n (%)** | 71 (51) | 36 (36) | 0.03 |
| **Loop diuretic, n (%)** | 105 (75) | 85 (86) | 0.04 |
| **Ivabradine, n (%)** | 21 (15) | 11 (11) | 0.38 |
| **Anticoagulation therapy, n (%)** | 73 (52) | 59 (58) | 0.33 |
| **Anti-platelet agent, n (%)** | 73 (52) | 55 (54) | 0.60 |
| **QRS morphology, n (%)** | | | |
| LBBB | 110 (78) | 82 (80) | 0.50 |
| RBBB | 10 (7) | 6 (6) | |
| NIVCD | 3 (2) | 0 | |
| Paced QRS | 18 (13) | 14 (14) | |
| **LVEF (%)** | 28 (6) | 28 (7) | 0.47 |
| **CRT-D, n (%)** | 122 (87) | 53 (52) | < 0,001 |
| **Upgrade, n (%)** | 41 (29) | 25 (25) | 0.43 |
| **Effectiveness, n (%)** | **70 (50)** | **48 (47)** | **0.69** |
| One-year survival | 124 (88) | 85 (83) | 0.31 |
| NYHA improvement | 86 (61) | 67 (66) | 0.72 |
| No admission for HF | 107 (76) | 71 (70) | 0.33 |
| **Complications, n in n patients (%)** | **55 in 30 (21)** | **27 in 15 (15)** | **0.19** |
| Reintervention, n (% of complications) | 24 (44) | 9 (33) | 0.07 |
| Lead displacement, n (%of complications) | 19 (34) | 7 (26) | 0.10 |
| Implantation failure, n (% of complications) | 3 (5) | 5 (19) | 0.23 |
| Infection, n (% of complications) | 6 (11) | 3 (11) | 0.59 |
| Pneumothorax, n (% of complications) | 2 (4) | 2 (7) | 0.74 |
| Perforating lead, n (% of complications) | 0 | 1 (4) | 0.24 |
| Pericardial effusion, n (% of complications) | 1 (2) | 0 | 0.39 |
| Hematoma, n (% of complications) | 0 | 0 | NA |

In univariate analysis, AF, CKD and rescue CRT were negatively associated with CRT response. Only AF and CKD remained predictors of CRT non-response in multivariate analysis in overall population. Moreover, AF negative impact was significant only in <75 years group (OR=0.28; CI 95% [0.13-0.62], p=0.001) but not in ≥75 years group. Defibrillator use was not associated with primary endpoint. Results of univariate and multivariate analyzes in ≥75 years group are listed in Table 2 and those in <75 years group in Table 3.

**Table 2: Univariate and multivariate analyzes of outcomes in the ≥75 years group**

Anticoagulation and atrial fibrillation were significantly correlated in ≥75 years group (Pearson coefficient 0.79, p<0.001). We performed two different regression models if p values were both <0.2 in univariate analysis. We reported here variables with p value ≤0.2 in univariate analysis and ≤0.10 in multivariate analysis. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease (defined by estimated glomerular filtration <60ml/mn/1.73m²); CRT: cardiac resynchronization therapy; CRT-D: CRT with defibrillator; NYHA: New-York Heart Association; OR: odds ratio

| | **Univariate analysis** | | **Multivariate analysis (model 1 with atrial fibrillation)** | | **Multivariate analysis (model 2 with anticoagulation)** | |
|---|---|---|---|---|---|---|
| **Primary endpoint** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| NYHA ≥III | 5.91 (2.02-17.30) | 0.001 | 6.02 (1.33-18.77) | 0.002 | 6.30 (2.04-19.67) | 0.001 |
| Rescue CRT | 0.49 (0.40-0.60) | 0.01 | | | | |
| CKD | 0.41 (0.16-1.03) | 0.06 | | | | |
| Loop diuretics | 0.32 (0.09-1.11) | 0.06 | | | | |
| Anticoagulation | 0.51 (0.23-1.15) | 0.10 | | | | |
| Atrial fibrillation | 0.51 (0.23-1.15) | 0.10 | | | | |
| ACEI-ARB | 2.07 (0.84-5.11) | 0.11 | 2.55 (0.91-7.11) | 0.07 | 2.38 (0.87-6.49) | 0.09 |
| Surgery duration | 1.87 (0.85-4.11) | 0.12 | | | | |
| QRS= 130-150ms | 0.50 (0.20-1.27) | 0.14 | | | | |
| **One-year mortality** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| Rescue CRT | 58.8 (6.55-528) | <0.001 | 44.67 (2.91-686) | 0.01 | 63.28 (4.47-896) | 0.002 |
| CRT-D | 0.23 (0.07-0.75) | 0.01 | | | | |
| Atrial fibrillation | 4.03 (1.07-15.20) | 0.03 | 6.72 (0.99-45.61) | 0.04 | | |
| QRS>150ms | 2.64 (0.86-8.15) | 0.08 | 3.79 (0.79-18.21) | 0.10 | | |
| Surgery duration | 0.39 (0.13-1.2) | 0.09 | 0.11 (0.02-0.63) | 0.01 | 0.14 (0.03-0.76) | 0.02 |
| CKD | 3.54 (0.75-16.67) | 0.09 | | | | |
| Upgrade | 0.36 (0.08-1.69) | 0.10 | | | | |
| Anticoagulation | 2.43 (0.72-8.13) | 0.14 | | | | |
| Beta-blockers | 0.42 (0.12-1.42) | 0.15 | | | | |
| Ivabradine | 2.63 (0.60-11.41) | 0.18 | 9.99 (1.17-85.42) | 0.04 | 6.36 (1.10-36.90) | 0.04 |
| ACEI-ARB | 0.47 (0.15-1.49) | 0.19 | | | | |

**Table 3: Univariate and multivariate analyzes of outcomes in <75 years group**

Anticoagulation and atrial fibrillation were significantly correlated in <75 years group (Pearson coefficient 0.69, p<0.001). We performed two different regression models if p values were both <0.2 in univariate analysis. We reported here variables with p value ≤0.2 in univariate analysis and ≤0.10 in multivariate analysis. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease (defined by estimated glomerular filtration <60ml/mn/1.73m²); CRT: cardiac resynchronization therapy; CRT-D: CRT with defibrillator; NYHA: New-York Heart Association; OR: odds ratio

| | **Univariate analysis** | | **Multivariate analysis** | | | |
|---|---|---|---|---|---|---|
| **Primary endpoint** | **OR (95% CI)** | **p** | **OR (95% CI)** | | **p** | |
| Atrial fibrillation | 0.36 (0.18-0.71) | 0.003 | 0.28 (0.13-0.62) | | 0.001 | |
| CRT-D | 2.39 (0.85-6.70) | 0.09 | | | | |
| Male gender | 2.39 (0.85-6.70) | 0.09 | | | | |
| CKD | 0.53 (0.26-1.07) | 0.08 | | | | |
| Ivabradine | 2.25 (0.85-5.97) | 0.10 | | | | |
| NYHA ≥III | 1.74 (0.89-3.41) | 0.11 | 2.09 (0.95-4.59) | | 0.07 | |
| QRS<130ms | 0.51 (0.21-1.24) | 0.13 | | | | |
| QRS>150ms | 1.63 (0.83-3.17) | 0.15 | | | | |
| | **Univariate analysis** | | **Multivariate analysis (model 1 with atrial fibrillation)** | | **Multivariate analysis (model 2 with anticoagulation)** | |
| **One-year mortality** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| Atrial fibrillation | 23.68 (3.04-184.30) | <0.001 | 14.35 (1.6-125.90) | 0.02 | | |
| Rescue CRT | 17.48 (4.97-61.44) | <0.001 | 14.32 (2.61-79.20) | 0.002 | 15.81 (3.35-75.10) | <0.001 |
| CRT-D | 0.11 (0.04-0.34) | <0.001 | | | | |
| Beta-blockers | 0.16 (0.05-0.51) | 0.001 | | | | |
| CKD | 5.93 (1.61-21.83) | 0.003 | 5.96 (1.13-31.30) | 0.04 | 7.65 (1.47-39.61) | 0.02 |
| Anticoagulation | 7.71 (1.68-33.26) | 0.003 | | | 5.32 (0.96-29.40) | 0.06 |
| ACEI-ARB | 0.26 (0.09-0.78) | 0.01 | | | | |
| Diabetes mellitus | 2.86 (1.02-8.01) | 0.04 | | | | |
| Loop diuretics | 5.67 (0.72-44.56) | 0.07 | | | | |
| NYHA ≥III | 4.24 (1.16-15.48) | 0.02 | | | | |
| QRS>150ms | 0.46 (0.15-1.38) | 0.16 | | | | |
| Complications | 2.06 (0.69-6.08) | 0.19 | 4.20 (0.91-18.91) | 0.07 | | |

**Secondary endpoints**

- *All-cause mortality*

At one-year, mortality rates were 12% and 17% in <75 and ≥75 years groups respectively (p=0.31). Survival curves are represented in Figure 1. Defibrillator use was associated with better survival in univariate analysis (p=0.01) but not after logistic regression. Multivariate analysis showed that rescue CRT (p=0.01 and 0.002 in ≥75 and <75 years group respectively) and AF (p=0.04 and 0.02 in ≥75 and <75 years groups respectively) were associated with mortality in both groups. CKD was predictive of one-year mortality only in <75 years group (p=0.04) whereas ivabradine use was associated with mortality only in ≥75 years group (p=0.04).

- *Complications*

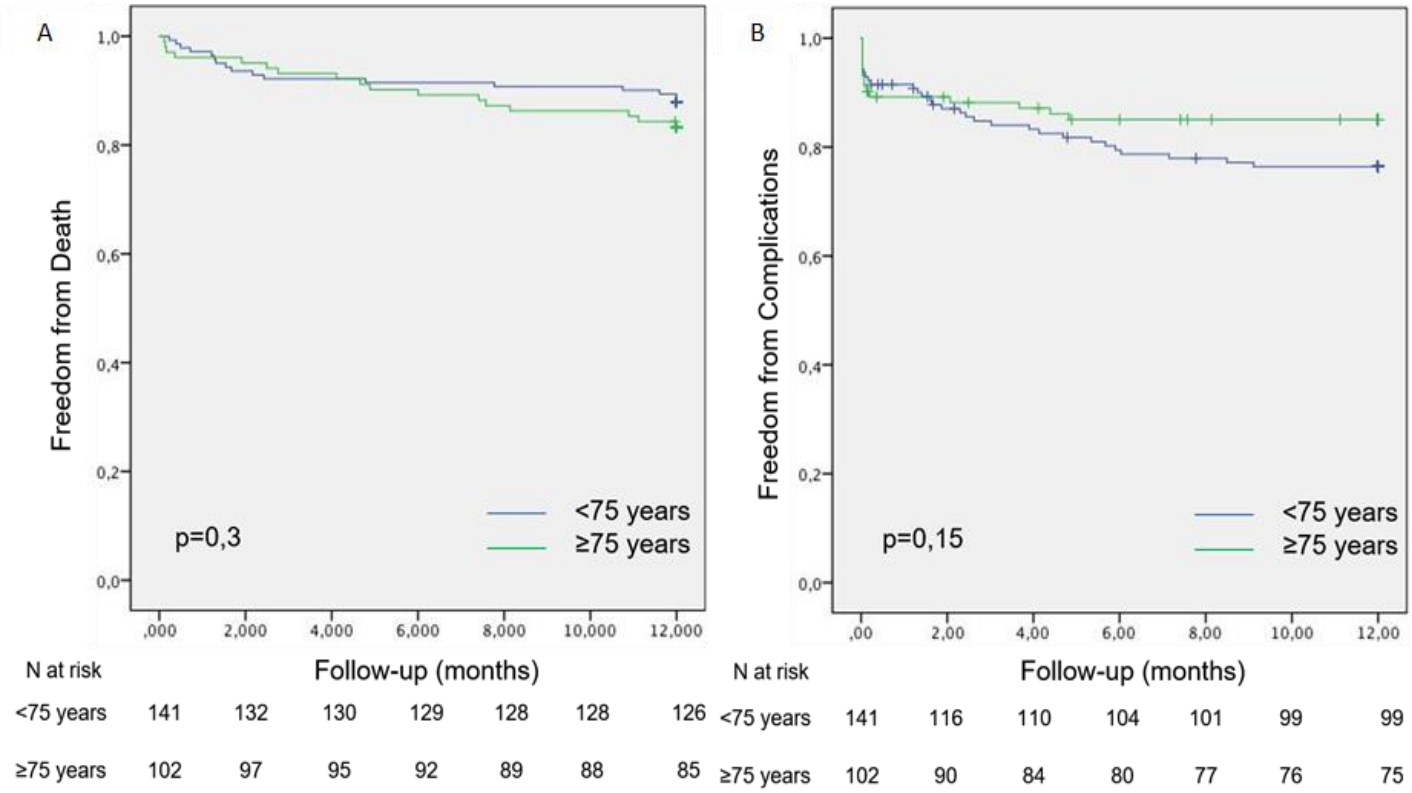
Eighty-two complications were reported in 45 patients (19%) of the study population. There was no difference in the one-year complications rates between age groups, 15% and 21% in ≥75 and <75 years groups respectively (p=0.19). Lead dislodgment and re-interventions were the most frequent issues with a trend toward a greater rate of reinterventions in <75 years group (p=0.07). Only defibrillator use (p=0.003) and QRS duration (p=0.02) were found independent predictive factors in overall population. There was no age-related predictor of complications.

- *Device therapies in patients with defibrillator (n=175)*

Nine (17%) patients ≥75 years experienced appropriate therapies compared to 11 (9%) patients <75 years (p=0.2). Only four patients, all in <75 years group, received inappropriate therapies.

**Figure 1: Kaplan-Meier curves for one-year mortality and complications in ≥75 and <75 years groups**

Panel A: Overall survival, Panel B: Complications. ≥75 years group is green and <75 years group is blue line. Comparisons were made with log-rank test.




| N at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| <75 years | 141 | 132 | 130 | 129 | 128 | 128 | 126 |
| ≥75 years | 102 | 97 | 95 | 92 | 89 | 88 | 85 |

| N at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| <75 years | 141 | 116 | 110 | 104 | 101 | 99 | 99 |
| ≥75 years | 102 | 90 | 84 | 80 | 77 | 76 | 75 |

## DISCUSSION

In our study, older patients with CRT presented more comorbidities than younger counterparts. Such differences were highlighted in others studies[4] and registries[3,10]. However, they were likely to respond to CRT as well as younger individuals, considering a clinical combined endpoint for CRT effectiveness defined as survival for one year with no heart failure hospitalization and improvement by ≥ one NYHA classes. Patients ≥75 years old with previous NYHA ≥III class were found to better respond than less symptomatic individuals whereas functional status was not predictive of CRT response in younger individuals. CRT was also

found to be safe in both age groups with no difference neither in mortality nor in complications rates. Strongest predictors of mortality, rescue CRT and AF, were not age-related.

Whether CRT could be as efficient in older patients as in younger remains uncertain. Observational studies[4,5,11,12] already showed that older patients are likely to respond to CRT as well as younger patients. In our study, age was not predictive of CRT response, as in a sub-analysis of two randomized trials comparing three age groups (<65; 65-75; >75 years) and reporting same improvements in LVEF and NYHA class regardless of age[13]. On the contrary, Maass et al. recently identified age <60 years as a predictive factor of reverse ventricular remodeling after CRT[14]. Little is known about response predictors according to age. We reported here for the first time that NYHA class ≥III at the time of implantation was associated with CRT response in the ≥75 years individuals but not in younger patients. Conversely, a recent study showed that NYHA class ≤III was an independent predictor of CRT benefit in a mid-sixties population[15]. On the contrary, AF has been associated with poor results of CRT[16]. In our study, this negative impact of AF was found in younger group whereas patients ≥75 years with AF improved as well as those in sinus rhythm.

There are conflicting results about CRT impact on mortality among older patients. We found no difference in mortality rates between age groups. This was also reported in limited studies[5]. Killu et al. showed after multivariate analysis no significant difference in survival between ≤80 and >80 years patients[6]. On the contrary, several authors pointed higher mortality rates among older patients[7,10,12,17] but with more non-cardiac death in these latter[17] and similar time to death between age groups[7]. Diabetes mellitus, CKD and low functional capacity were predictive of worse survival in ≥75 years patients during long-term follow-up[17]. In our study we found that one-year mortality was strongly associated with rescue CRT and AF, which were not age-related. CKD was not associated with mortality in ≥75 age group but only in younger patients. The COMPANION trial reported that CRT reduced all-causes mortality only in defibrillator group[18], whereas defibrillator use was not associated with survival neither in <75 nor in ≥75 years patients in our study. We also found that ivabradine use was predictive of death in older

patients. We have no explanation for this finding that hasn't been reported before and could be hazard-related. On the contrary, a recent study showed that ivabradine was well-tolerated in patients ≥70 years with systolic HF[19].

There was no difference concerning complications after CRT implantation between age groups. Despite higher rates of comorbidities and advanced HF, age ≥75 years wasn't associated with higher complications rates. This is consistent with most of published data[5,10]. Höke et al reported only a trend toward higher incidence of pneumothorax and pocket hematoma in ≥75 years patients[17]. Nevertheless, risk of adverse events is the most frequent reported explanation for CRT age-limit observed in European centers[20]. As reported recently[21], we found that CRT defibrillator was more associated with complications than CRT pacemaker regardless of age.

Thus, our results support that CRT is essential for older adults. Those patients are difficult to "optimize" because of CKD and hypotension limiting medical therapy, disabilities limiting cardiac rehabilitation and others age-related features defining elderly's frailty. Patients over 75 years, with advanced HF and high NYHA class, even with AF, should be considered for CRT. Age should not be a limit itself but individual risk has to be evaluated thanks to other comorbidities to decide CRT implantation whether associated or not with defibrillator.

**Limits**

Some limits of our study should be addressed. This retrospective study with a small sample size may be underpowered and subject to selection bias. Except in case of rescue CRT, we can assume that the frailest elderly patients were not implanted and this could lead to overestimate CRT benefit among the ≥75 years. Causes of death weren't adjudicated and therefore not analyzed. Last, we didn't retrieve cognitive status, quality of life score and end-of-life experiences whereas these outcomes are at great concerns especially for the older patients[2]. Further studies should be designed to address these differences in outcomes predictors between younger and older patients with CRT.

## CONCLUSION

Our study showed that very symptomatic older adults are likely to respond to CRT and that AF was not associated with worse outcomes. We also highlighted safety and efficiency of CRT regardless of patients' age.

## LIST OF ABBREVIATIONS

AF: Atrial fibrillation

CKD: Chronic kidney disease

CRT: Cardiac resynchronization therapy

HF: Heart failure

LBBB: Left-bundle branch block

LVEF: Left ventricular ejection fraction

NYHA: New-York Heart Association

## DECLARATIONS

### Ethics approval and consent to participate

This retrospective study based on previous collected data complied with standards of Méthodologie de référence (MR-004) defined by Commission Nationale Informatique et Libertés and published in Journal Officiel de la République Française (JORF n°0160 du 13 juillet 2018 : Délibération n° 2018-155 du 3 mai 2018 portant homologation de la méthodologie de référence relative aux traitements de données à caractère personnel mis en œuvre dans le cadre des recherches n'impliquant pas la personne humaine, des études et évaluations dans le domaine de la santé (MR-004). Patient's consent is not required for this study type.

### Consent for publication

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

Authors have no conflict of interest regarding this study.

**Funding**

This study received no funding.

**Authors' contributions**

LCR, ALC, PO, MC, AP, DL, PM conceived and designed the research. LCR, ALC, PO, MC, AP, DL collected and analyzed data. PO, LCR, ALC performed statistical analysis. LCR, ALC, PM wrote manuscript. All authors made critical revision of the manuscript and approved the final version. LCR and ALC contributed equally.

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Not applicable

## REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–200.

2. Kramer DB, Reynolds MR, Mitchell SL. Resynchronization: considering device-based cardiac therapy in older adults. *J Am Geriatr Soc* 2013;**61**:615–21.

3. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, *et al.* The European cardiac resynchronization therapy survey. *Eur Heart J* 2009;**30**:2450–60.

4. Delnoy PPHM, Ottervanger JP, Luttikhuis HO, Elvan A, Misier ARR, Beukema WP, *et al.* Clinical response of cardiac resynchronization therapy in the elderly. *Am Heart J* 2008;**155**:746–51.

5. Foley PWX, Chalil S, Khadjooi K, Smith REA, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronization therapy in octogenarians: a comparative study with a younger population. *Europace* 2008;**10**:1302–7.

6. Killu AM, Wu J-H, Friedman PA, Shen W-K, Webster TL, Brooke KL, *et al.* Outcomes of cardiac resynchronization therapy in the elderly. *Pacing Clin Electrophysiol* 2013;**36**:664–72.

7. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J, *et al.* Response to cardiac resynchronization therapy in elderly patients (≥70 years) and octogenarians. *Eur J Heart Fail* 2013;**15**:203–10.

8. Rickard J, Cheng A, Spragg D, Green A, Leff B, Tang W, *et al.* Survival in octogenarians undergoing cardiac resynchronization therapy compared to the general population. *Pacing Clin Electrophysiol* 2014;**37**:740–4.

9. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.

10. Suleiman M, Goldenberg I, Haim M, Schliamser JE, Boulos M, Ilan M, *et al.* Clinical characteristics and outcomes of elderly patients treated with an implantable cardioverter-defibrillator or cardiac resynchronization therapy in a real-world setting: data from the Israeli ICD Registry. *Heart Rhythm* 2014;**11**:435–41.

11. Brambatti M, Guerra F, Matassini MV, Cipolletta L, Barbarossa A, Urbinati A, *et al.* Cardiac resynchronization therapy improves ejection fraction and cardiac remodelling regardless of patients' age. *Europace* 2013;**15**:704–10.

12. Achilli A, Turreni F, Gasparini M, Lunati M, Sassara M, Santini M, *et al.* Efficacy of cardiac resynchronization therapy in very old patients: the Insync/Insync ICD Italian Registry. *Europace* 2007;**9**:732–8.

13. Kron J, Aranda JM, Miles WM, Burkart TA, Woo GW, Saxonhouse SJ, *et al.* Benefit of cardiac resynchronization in elderly patients: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. *J Interv Card Electrophysiol* 2009;**25**:91–6.

14. Maass AH, Vernooy K, Wijers SC, Sant J van 't, Cramer MJ, Meine M, *et al.* Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study. *Europace* 2018;**20**:e1–10.

15. Providencia R, Marijon E, Barra S, Reitan C, Breitenstein A, Defaye P, *et al.* Usefulness of a clinical risk score to predict the response to cardiac resynchronization therapy. *Int J Cardiol* 2018;**260**:82–7.

16. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, *et al.* Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2012;**5**:566–70.

17. Höke U, Putter H, Van Der Velde ET, Schalij MJ, Delgado V, Bax JJ, *et al.* Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. *Circ Cardiovasc Qual Outcomes* 2014;**7**:437–44.

18. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.

19. Zachariah D, Stevens D, Sidorowicz G, Spooner C, Rowell N, Taylor J, *et al.* Quality of life improvement in older patients with heart failure initiated on ivabradine: Results from the UK multi-centre LIVE:LIFE prospective cohort study. *Int J Cardiol* 2017;**249**:313–8.

20. Chen J, Hocini M, Larsen TB, Proclemer A, Sciaraffia E, Blomström-Lundqvist C, *et al.* Clinical management of arrhythmias in elderly patients: results of the European Heart Rhythm Association survey. *Europace* 2015;**17**:314–7.

21. Barra S, Providência R, Boveda S, Duehmke R, Narayanan K, Chow AW, *et al.* Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. *Heart* 2018;**104**:1529–35.

## 4ème partie : Les nouvelles technologies de cartographie électro-anatomique permettent-elles d'améliorer, sans surrisque, les résultats de l'ablation des troubles du rythme supra-ventriculaires complexes chez les patients IC ?

Dans cette dernière partie, nous nous sommes intéressés au résultat de l'ablation RF des arythmies supraventriculaires complexes chez des patients en IC et à l'intérêt d'un nouveau système de CEA dans cette population.

Nous avons, pour cette partie, collaboré avec le Pr Maury du CHU de Toulouse. La première étape de ce travail a consisté à comparer les résultats obtenus avec le système de CEA ultra-haute densité (UHD) Rhythmia™ (Boston Scientific, Malborough, USA) avec ceux obtenus avec des systèmes conventionnels sur l'ablation de TA, chez des patients non sélectionnés. Nous avons comparé 60 procédures réalisées avec l'aide du système Rhythmia™ à 60 procédures réalisées à l'aide d'autres systèmes de cartographie. Les procédures réalisées avec le système UHD étaient un peu plus longues (p=0.07), sans différence de durée de fluoroscopie ni de cartographie, alors que le nombre de cartes (p=0.001) et d'électrogrammes acquis (p<0.001) étaient significativement plus élevés. Les taux de succès immédiats étaient équivalents entre les groupes. Cependant nous avons mis en évidence un taux de récidive d'arythmies à un an plus faible dans le groupe Rhythmia™ (37%) comparé aux autres systèmes (51%), p=0.046. Les taux de complications étaient quant à eux comparables dans les deux groupes. Ce premier travail a donc montré un bénéfice potentiel à l'utilisation du système Rhythmia™ sur le maintien en rythme sinusal chez des patients traités pour des TA.

Pour poursuivre cette première étude, nous avons voulu analyser la faisabilité et l'efficacité de l'utilisation du système Rhythmia™ pour guider des procédures d'ablation RF de FA et de TA chez des patients IC. Nous avons inclus toutes les procédures d'ablation FA/TA réalisées aux CHU de Caen et de Toulouse entre 2015 et 2018, guidées par le système Rhythmia™, chez

des patients IC, comparés à des patients non-IC. Nous avons donc retenu 296 procédures réalisées chez 246 patients, parmi lesquels 135 (170 procédures) avaient un antécédent d'IC clinique et/ou une FEVG <50% et ont constitués le groupe IC, les 111 patients restants (126 procédures) formaient le groupe non-IC. Le critère principal de sécurité était la survenue de décès ou de complications liés à la procédure. Le critère principal d'efficacité était la récidive de FA/TA à un an. Les critères secondaires étaient les caractéristiques des procédures, le succès immédiat, les hospitalisations pour IC, l'amélioration du stade NYHA et de la FEVG à un an. Les patients du groupe IC étaient plus âgés, présentaient plus de comorbidités, avaient une FEVG plus basse, un stade NYHA plus élevé, et recevaient plus de médicaments de l'IC que les patients du groupe non-IC. Un total de 13 procédures ont été suivies de complications, 8 dans le groupe IC (5,3%) et 5 dans le groupe non-IC (4,8%, p=1,000). Aucun décès lié aux procédures n'a été rapporté. Nous n'avons pas mis en évidence de facteur prédictif de complications, en dehors d'une tendance à un âge plus élevé chez les patients ayant eu des complications (p=0,051). Le taux de récidives de FA/TA à un an était de 31,9% dans le groupe IC et de 25,2% dans le groupe non-IC (p=0,262), avec un taux de reprise de 17,1%. Les facteurs associés à la récidive d'un trouble du rythme en analyse multivariée étaient la présence d'une fuite mitrale (p=0,011), d'une cardiomyopathie hypertrophique (p=0,011), et d'une FA persistante (p=0,02). Les procédures des patients IC étaient plus longues, avec des durées de fluoroscopie et de cartographie plus importantes, avec des taux de succès immédiat identiques dans les deux groupes. Le seul facteur prédictif indépendant d'hospitalisations pour IC était l'appartenance au groupe IC (p=0,002), alors qu'il y avait une tendance à l'augmentation du risque d'hospitalisations en cas de récidive de FA/TA (p=0,078). Les patients du groupe IC ont significativement amélioré leur classe NYHA et leur FEVG comparés aux patients non-IC. Chez les patients IC, la récurrence de FA/TA était associée de façon significative à l'absence d'amélioration fonctionnelle. Au sein du groupe IC, les patients ayant une FEVG altérée <50% n'ont pas subi plus de complications que ceux ayant une FEVG ≥50% (p=0,469), et leurs taux de maintien du rythme sinusal à un an étaient également équivalents (26,4% versus 37,1%, p=0,196). Les patients IC ayant une FEVG altérée ont significativement

plus souvent amélioré leur FEVG que les patients à FEVG préservée (p=0,002), mais sans plus améliorer leur classe NYHA (p=0,49).

Ces travaux ont permis de montrer que les procédures d'ablation complexes de FA/TA guidées par un système de cartographie UHD n'étaient pas plus à risque de complications chez des patients IC, que la FEVG soit altérée ou préservée, que chez des patients contrôles, et qu'elles permettaient d'obtenir chez ces individus fragiles un taux de maintien en rythme sinusal à un an équivalent, accompagné d'une amélioration fonctionnelle et d'un remodelage favorable.

**Articles :**

1) Maury P*, **Champ-Rigot** L*, Rollin A, Mondoly P, Bongard V, Galinier M, Carrié D, Marminia E, Capellino S, Marty L, Milliez P.

*Comparison between novel and standard high-density 3D electro-anatomical mapping systems for ablation of atrial tachycardia.*

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2) **Champ-Rigot L**, Marminia E, Ollitrault P, Rollin A, Pellissier A, Chequel M, Maury P, Milliez P.

*Safety and acute results of ultra-high density mapping to guide catheter ablation of atrial arrhythmias in heart failure patients*

3) **Champ-Rigot L**, Marminia E, Ollitrault P, Rollin A, Pellissier A, Chequel M, Maury P, Milliez P.

*Long-term clinical outcomes after catheter ablation of atrial arrhythmias guided by ultra-high density mapping system in heart failure patients*

# Comparison between novel and standard high-density 3D electro-anatomical mapping systems for ablation of atrial tachycardia

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Disclosures : none (except for S. Capellino who is employed by Boston Scientific)

No other competing financial interests.

## ABSTRACT

**Background:** Ultra high-density mapping allows very accurate characterization of circuits/mechanisms in atrial tachycardia (AT). Whether these advantages will translate into a better procedural or long-term clinical outcome is unknown.

**Methods:** Sixty consecutive AT ablation procedures using ultra-high density mapping (Rhythmia™, group 1) were retrospectively compared to 60 consecutive procedures using standard high density mapping (Carto/NavX™ , group 2) (total 209 AT, 79 % left AT).

**Results :** A higher number of maps were performed in group 1 (4.8±2.5 vs 3.2±1.7, p=0.0001) with similar acquisition duration (12±5 vs 13±6 min per map, p=ns) although with a greater number of activation points (10543±5854 vs 689±1827 per map, p<0,0001). AT location remained undetermined in 5 AT in group 1 vs 10 (p=0.1). Mechanism remained undetermined in 5 AT from group 1 vs 11 (p=0.06). Acute complete success was achieved in 77 %, in both groups. At one year follow-up, AT recurred in 37% in group 1 vs 50% in group 2 (p=0.046).

**Conclusion:** There are less long-term recurrences after AT ablation using ultra high-density mapping system compared to standard high-density three-dimensional mapping, possibly because of a better comprehensive approach of AT mechanisms.

**KEYWORDS :** atrial tachycardia, mapping, 3D electro-anatomical system, ablation

## INTRODUCTION

Mechanisms and anatomical locations of atrial tachycardia (AT) have been widely investigated over previous decades [1, 2]. Understanding of these mechanisms and anatomical characteristics has dramatically increased with the advent of three-dimensional (3D) navigation mapping systems [3, 6]. Such navigation mapping systems reconstruct 3D left or right atrial anatomy while adding some informations about activation (propagation of the depolarisation wavefront) of the atrial myocardium during AT. Increasingly complex mechanisms have been elucidated, leading to more complex ablation strategies, especially for AT occurring after previous ablation of atrial fibrillation (AFib) [2], after cardiac surgery [7] or in patients with surgically palliated congenital heart disease [5, 8-10].

Standard usual 3D electro-anatomical mapping systems are sometimes of limited help for very complex AT mechanisms, and ablation strategies based on these systems may offer varying success rates (from 73 to 100%) and relatively high recurrence rates (up to 53%) [1, 3, 5, 7, 9-14]. More sophisticated 3D systems with high-density mapping are currently used, although with still imperfect results [4].

A novel high-density 3D mapping system (Rhythmia™, Boston Scientific Inc.) seems to offer more detailed insight into activation/mechanisms because of the density of recorded electrograms, the reliability of electrograms annotation, low noise and enhanced characteristics of recording [15]. Recent reports demonstrated the possibility of very accurate characterization of AT circuits using the Rhythmia™ system [16] which may even allow correction of erroneous evaluations of AT mechanisms made by other systems [17]. However, whether these advantages will translate into a better procedural or long-term clinical outcome is unknown.

The aim of this study was to compare procedural parameters as well as acute and long-term outcomes of AT ablation using standard (Carto™, NavX™) versus Rhythmia™ 3D high-density

mapping systems. We hypothesized that ultra-high density mapping may lead to more efficient ablation and better outcome.

## METHODS

We conducted a retrospective study comparing consecutive patients presenting for AT ablation with the Rhyhmia ™ system to those using the standard 3D mapping systems (Carto ™ and NavX ™) over the same period of time. This study was performed in both University Hospitals of Toulouse and Caen from 2015-2016. Use of 3D mapping system was randomly allocated, every operator/center using both systems without any preference or reason of choice at this time. Only patients referred for scheduled AT ablation were included. Ablation procedures for scheduled typical atrial flutter or AFib were not considered, as well as AT occuring during AFib ablation. For patients investigated with the Rhythmia™ system (n=60), mapping was performed using the Intella Map Orion™ catheter [15, 18] which is an 8-splines expandable basket-like catheter including 64 mini-electrodes (0.4 $mm^2$, 2.5 mm inter-electrode distance). For the procedures involving the Carto 3 ™ system (n=38), mapping was also performed with multipolar electrode catheters (Lasso-NaV™ with 10 to 20 electrodes or PentaRay-Nav™ with 20 electrodes). Automatical annotation system (Confidense™) was used in 18 procedures, otherwise points were manually acquired. Manual points acquisition was also performed with similar multipolar catheters (Lasso Biosense™ or Spiral St Jude™ with 10 to 20 electrodes) in patients investigated with the NavX™ Velocity system (n=22). For the 60 Rhythmia™ based procedures, radio-frequency (RF) ablation was performed with standard irrigated 4 mm-tip catheters (Cordis Thermocool ™ n=51, Boston Blazer OI ™ n=9), while contact-force irrigated 4 mm-tip catheters (Biosense Thermocool Smarttouch ™ or St-Jude TactiCath ™) were used for every Carto ™ and for most NavX ™ based procedures (Cordis Thermocool ™ n=5 and St-Jude Coolflex ™ n=2 in the remaining ones)**.** AT mechanism was investigated by carefully analyzing activation in every case without entrainment mapping. Mechanisms of AT were defined as focal (concentric activation of the whole atrium from one localized area without

returning wavefront to this area), localized reentry (recording of a full reentry circuit not related to macro-reentry) and macro-reentry (recording of a full reentry circuit including the LA roof and/or the mitral isthmus). True determination of the mechanism/location of each AT was defined by the interruption of the AT during RF application at a critical site determined by the system (either resumption of sinus rhythm or abrupt change in AT rate and/or atrial activation), otherwise mapping was continued until better delineation of the AT mechanism.

Complete success of the ablation procedure was defined by the elimination of all successive mapped AT with resumption of sinus rhythm, while partial success was defined by the elimination of the clinical AT only (with failure to ablate other AT). Failure of the procedure was defined by the inability to ablate the clinical AT. Bidirectional conduction block across linear lesion sets were checked and eventually completed. For avoiding induction of AT of uncertain significance, attempts to reinduce AT or use of isoproterenol were not routinely performed after resumption of sinus rhythm by ablation.

Clinical outcome was assessed in all patients by retrospectively retrieving consultation or hospitalization files, or by contacting the patients/physicians to determine freedom from recurrence. Informations about recurrence of AT or AFib were assessed by ECG documentation or 24-hours ambulatory recording as needed in case of palpitations. Informed consent was obtained from all patients and the study has been performed in accordance with ethical standards and declared to the CNIL (Commission Nationale de l'Informatique et des Libertés) according to the french law.

**Statistical analysis**

Categorical variables were described as numbers and percentages and compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as mean ± standard deviation and compared using unpaired t-test. Logistic regression was performed for determining the parameters associated with the recurrence of AT. Parameters

significantly related to recurrence in univariate analysis were considered as eligible explanatory variables in a full multivariate logistic model. The Kaplan–Meier method was used to generate actuarial arrhythmia-free survival curves for each group. Events were censored at the time of first recurrence and follow-up duration was one year for any patient (no patient was lost to follow-up). Differences between groups were assessed with the Breslow-Gehan-Wilcoxon test. Because only a few patients had more than one procedure, for clearer presentation of the results, each procedure was considered as a different patient. Analysis and calculations were performed using StatView™ program (Abacus Concepts, Inc. Berkeley, CA 1992-1996, version 5.0). A p value $\leq$0.05 was considered statistically significant for each analysis.

## RESULTS

### Population characteristics

Sixty consecutive procedures (56 patients) using the Rhythmia ™ system (group 1) were compared to 60 consecutive procedures (55 patients) using the Carto/NavX ™ systems (group 2). Exemples of activation map during AT with the Rhythmia ™ and Carto ™ systems are shown in Figures 1 and 2. Characteristics of the patient population are depicted in Table 1. There was no significant difference between groups, except for a moderately lower LVEF in group 2 patients (46±16 vs 52±13, p=0.04). Almost all patients had been unsuccessfully treated by anti-arrhythmic drugs, with beta-blockers in two thirds and amiodarone in half. A history of previous AFib ablation was noted in the majority of patients, slightly more in group 1 compared to group 2 patients (75 vs 58%, p=0.05). Previous AFib ablation included pulmonary vein isolation in all, with or without additional linear and/or substrate ablation. Forty-four patients (37%) already underwent previous AT ablation and thirty patients (25%) had undergone previous cardiac surgery with either RA or LA incisions, without difference between

groups. Repaired congenital heart diseases were present in 10 cases (8%) without significant difference between groups, mainly represented by surgical closure of atrial septal defects.

**Figure 1: Right anterior view of an activation map of a left AT investigated with the Rhythmia™ 3D electro-anatomical system, showing a localized re-entry at the low septal aspect of the left atrium (white arrows) with collision of bystander wavefronts outside the circuit (black arrows)**

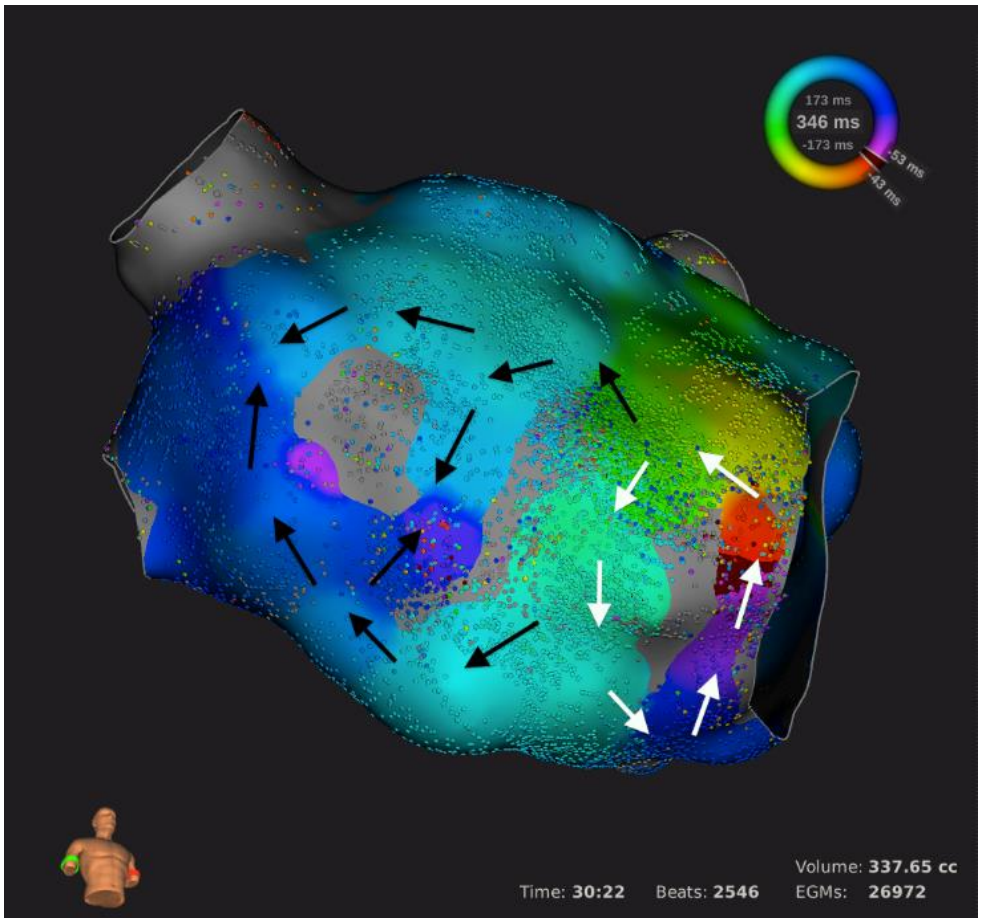


**Figure 2: Posterior view of an activation map of a left AT investigated with the Carto™ 3D electro-anatomical system, showing a large macroreentry through the roof of the left atrium and with a large descending wavefront over the posterior wall**

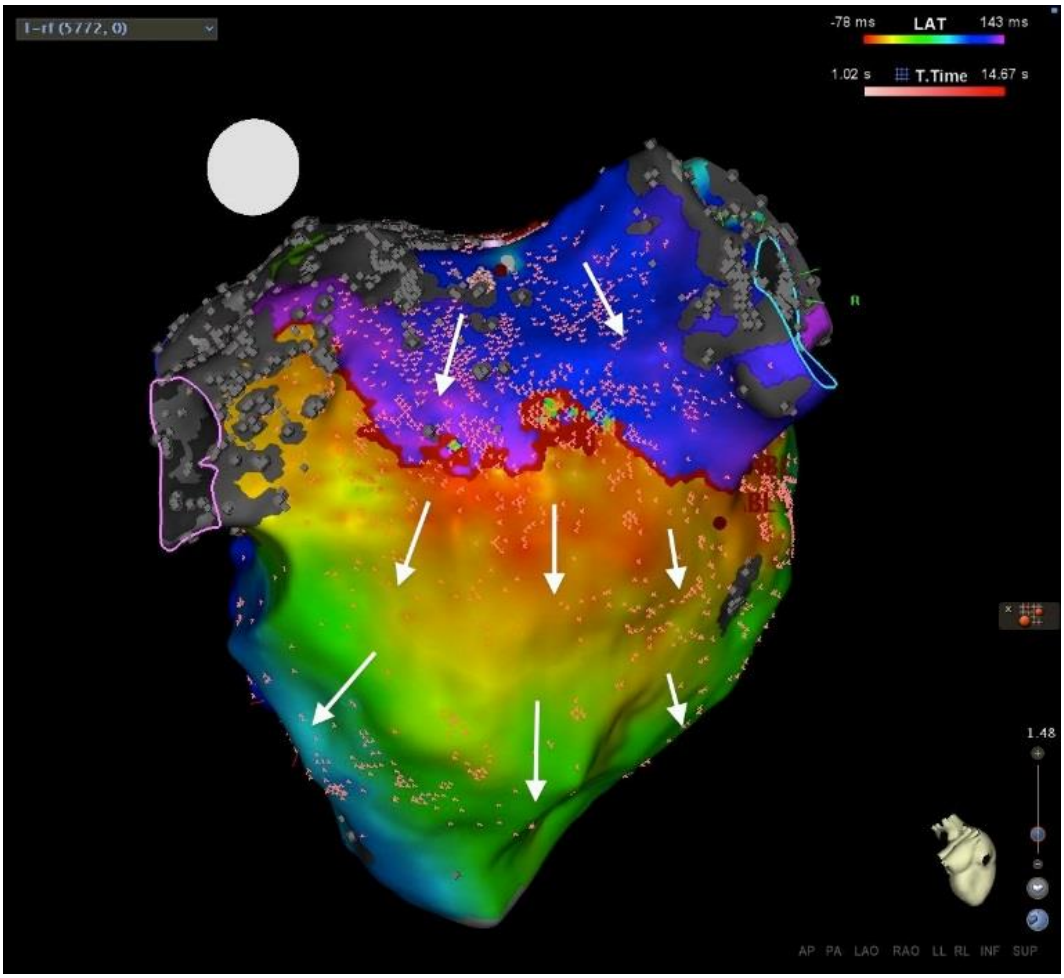


**Table 1 : Clinical characteristics of the population**

AF: atrial flutter, AFib: atrial fibrillation, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, PV: pulmonary veins

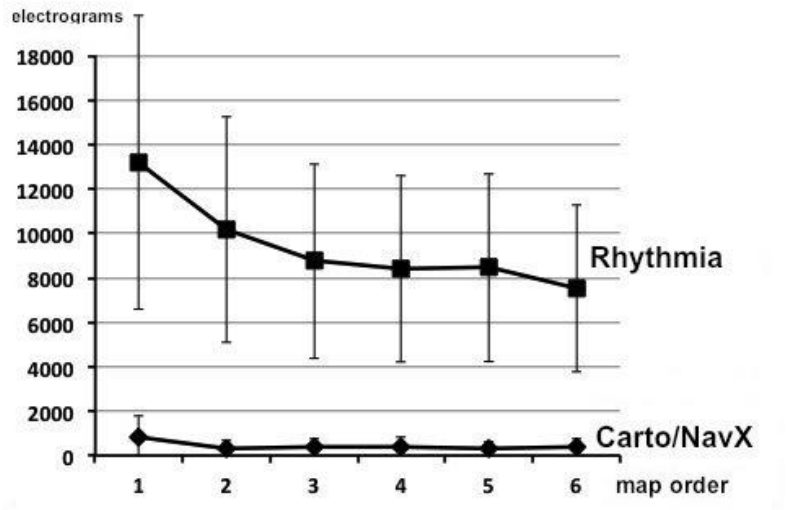
| | **Total n = 120** | **Rhythmia ™ n = 60** | **Carto/Navx ™ n = 60** | **p** |
|---|---|---|---|---|
| **Age (years)** | 64 ± 11 | 63 ±11 | 64 ±11 | ns |
| **Male gender** | 92 (77%) | 46 (77%) | 46 (77%) | ns |
| **Hypertension** | 68 (57%) | 34 (57%) | 34 (57%) | ns |
| **Diabetes** | 20 (17%) | 7 (12%) | 13 (22%) | ns |
| **Left atrium area (cm²)** | 27 ± 8 | 26 ± 9 | 28 ±7 | ns |
| **LVEF (%)** | 49 ±15 | 52 ±13 | 46 ±16 | 0.04 |
| **Heart failure** | 64 (53%) | 30 (50%) | 34 (57%) | ns |
| **Structural heart disease** | 96 (80%) | 47 (78%) | 49 (82%) | ns |
| **NYHA class** | | | | |
| I | 32 (27%) | 20 (33%) | 12 (20%) | |
| II | 60 (50%) | 27 (45%) | 33 (55%) | ns |
| III | 21 (17%) | 9 (15%) | 12 (20%) | |
| IV | 7 (6%) | 4 (7%) | 3 (5%) | |
| **Anti-arrhythmic drug** | 115 (96%) | 57 (95%) | 58 (97%) | ns |
| beta-blocker | 79 (66%) | 38 (63%) | 41 (68%) | ns |
| Ca channel blocker | 7 (6%) | 4 (7%) | 3 (5%) | ns |
| amiodarone | 64 (53%) | 32 (53%) | 32 (53%) | ns |
| classe 1 drug | 7 (6%) | 4 (7%) | 3 (5%) | ns |
| sotalol | 6 (5%) | 4 (7%) | 2 (3%) | ns |
| **Paroxysmal AFib** | 24 (20%) | 13 (22%) | 11 (18%) | ns |
| **Persistent AFib** | 89 (74%) | 45 (75%) | 44 (73%) | ns |
| **Previous typical AF** | 46 (38%) | 23 (38%) | 23 (38%) | ns |
| **Previous AFib ablation** | 80 (67%) | 45 (75%) | 35 (58%) | **0.05** |
| linear ablation | 65 (82%) | 36 (82%) | 29 (83%) | ns |
| PV isolation | 78 (98%) | 43 (97%) | 35 (100%) | ns |
| defragmentation | 61 (81%) | 38 (86%) | 23 (74%) | ns |

**Ablation procedures**

Procedural durations were slightly longer in group 1 (216±66 vs 195±61 min, p=0.07), while fluoroscopy duration did not significantly differ (29±16 vs 25±12 min, p=0.15). A higher total number of maps were performed in group 1 patients (4.8±2.5 vs 3.2±1.7, p=0.0001), represented by a higher number of activation maps (3.6±2.3 vs 2.7±1.5, p=0.017) and a higher number of maps for assessing linear lesions (1.2±1.6 vs 0.5±1.1, p=0.007). Total

duration of map acquisition was longer in group 1 (49±21 vs 41±17 min) although not significantly (p=0.1), but mean map acquisition duration did not differ (12±5 vs 13±6 min per map, p=ns). A much greater number of activation points were recorded in group 1 : total 23255±9828 vs 1542±2138, and 10543±5854 vs 689±1827 per map (p<0,0001 for each comparison). As a rule, for each patient, after the first map, progressively less activation points were recorded in the following successive maps. Changes in the number of recorded points according to the map order in each group are shown in Figure 3.

**Figure 3: Changes in the number of recorded electrograms according to the map order in each group. Even after repeated maps, the number of activation points remains very high in the Rhythmia ™ group**




**AT characteristics**

A total of 209 ATs were mapped: 112 in group 1 and 97 in group 2, from one to six per procedure (mean 1.7±0.9) (1.9±1.1 in group 1 and 1.6±0.8 in group 2, p=ns). One hundred sixty-six ATs originated from the LA (79 %) and 43 from the right atrium (RA) (21 %). The majority of right AT mechanisms were typical atrial flutter (n=24, 56%) and the majority of left AT were peri-mitral reentry (n=33, 20%), roof-dependent AT (n=31, 19%) and pulmonary vein

AT (n=19, 11%) (see Table 2). There were more left AT (87%) in group 1 vs group 2 (71%) (p=0.006), but there was no significant difference according to the various locations of AT (p=0.3) although more typical atrial flutters were present in group 2 and more mitral/roof dependent ATs were present in group 1) (Table 2). Precise location of AT circuit/focus remained undetermined in 15 cases (8%) (5 in group 1 and 10 in group 2, p=0.1). AT mechanisms were macro-reentry in 100 (48%), localized reentry in 69 (33%), focal in 24 (11%) and remained undetermined in 16 (8%). There were significantly less focal (n=8) and more macro reentry mechanisms (n=66) diagnosed in patients investigated with the Rhythmia™ system compared to Carto/NavX™ group (n=16 and 34 respectively), while localized reentry were equally found in both groups (n= 33 and 36 respectively) (p=0.004 for global comparison). Precise mechanism remained undetermined in 5 AT from group 1 vs 11 from group 2 (p=0.06).

**Table 2 : locations of AT**

Patients with previous ablation of typical atrial flutter presented with left AT (n=40, 87%) but also right AT (n=5, 11%) and recurrent common atrial flutter (n=6, 13 %). For left AT, we observed macro reentry using the mitral isthmus in 11 and the roof in 12, and other localized reentry of focal left AT from various locations in 26

| **Right AT** | **n=43<br>15 (group I) vs 28 (group II)** | **Left AT** | **n=166<br>97 (group I) vs 69 (group II)** |
|---|---|---|---|
| Typical Atrial flutter | n=24<br>7 vs 17 | Mitral isthmus dep AT | n=33<br>23 vs 10 |
| Crista terminalis | n=9<br>5 vs 4 | Roof dependant AT | n=31<br>19 vs 12 |
| Right appendage | n=4<br>1 vs 3 | Pulmonary veins | n=19<br>13 vs 6 |
| Other right AT | n=3<br>1 vs 2 | Septum | n=17<br>9 vs 8 |
| Undetermined right AT | n=3<br>1 vs 2 | Anterior LA | n=11<br>5 vs 6 |
| | | Left appendage | n=11<br>7 vs 4 |
| | | Posterior LA | n=10<br>5 vs 5 |
| | | LA floor | n=10<br>5 vs 5 |
| | | Coronary sinus | n=5<br>3 vs 2 |
| | | Other left AT | n=7<br>4 vs 3 |
| | | Undetermined left AT | n=12<br>4 vs 8 |

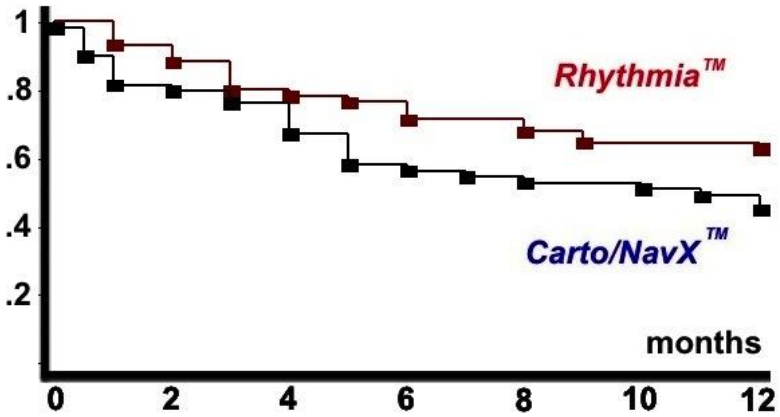
**Procedural success and complications**

RF duration did not differ between groups (27±17 vs 27±22 min, p=ns). Complete success was achieved in 92 procedures (77% in both groups), partial success was noted in 19 procedures (16%) (18 vs 13% in group 1 and group 2) while failure to ablate the clinical AT was observed in 9 procedures (7%) (5 vs 10%) (p=ns). Major complications occurred in one patient from group 1 (tamponade) vs none in group 2 (p=ns). Minor complications (non-surgical vascular complications or asymptomatic pericardial effusions) happened in 12 and 15 patients respectively (p=ns).

**Long-term follow-up**

At one-year follow-up, 22 patients in group 1 presented with recurrent ATs (37%) vs 31 in group 2 (51%) (p=0.046). AT-free survival curves are displayed in Figure 4. Five patients presented with AFib at one year (three in group 1 and two in group 2, p=ns). These patients did not experience recurrent AT, while patients with a relapse of AT did not present with AFib.

**Figure 4 : AT-free survival curves showing less AT recurrence with the Rhythmia™ mapping system over time (p=0.05)**



## DISCUSSION

Due to the various anatomical substrates or mechanisms involved, ablation of AT has lower success rates than for typical atrial flutter [1]. The progressive inclusion of increasingly complex AT have led to more complex procedures, especially for AT recurring after AFib ablation, cardiac surgery or in operated congenital heart disease, hampering the success rate of ablation [2, 5, 7, 8-10].

Although randomized comparison of 3D mapping systems against conventional electro-physiological fluroscopic procedures failed to demontrate any superiority in acute outcome [6, 19], these techniques are currently used worldwide and allow more detailed activation and better understanding of underlying complex mechanisms [3-6, 19]. However, standard 3D mapping systems (Carto™ or Ensite NavX™) are sometimes of limited help for very complex AT, and ablation based on these systems may offer non optimal success rates [7, 9, 20], even using high-density mapping [4], while recent studies demontrated the acute and long-term benefits of ultra high density mapping compared to conventional point by point 3D mapping in AT [21].

The Rhythmia™ system offers enhanced features for recording and annotation of electrograms [15]. Very accurate diagnosis of AT circuit or mechanism has been demonstrated using this system [16], which may be even able to correct erroneous interpretations resulting from use of other systems [17]. However whether these advantages translate into a better procedural or long-term clinical outcome remained to be proved.

In this study, we found that ablation based on ultra high-density mapping as allowed by the Rhythmia™ system offers more detailed insight into activation/mechanisms and improved long-term success rates compared with conventional high density 3D mapping systems. To the best of our knowledge, no previous study had been dedicated to compare long-term efficiency of different 3D systems.

We also found that procedural durations were slightly longer with the Rhythmia™ system, but without either an increased duration of fluoroscopy, RF delivery or complication rate. This was related to the higher number of maps recorded with the Rhythmia™ system, as mean durations of map acquisition were not significantly longer despite a higher number of recorded electrograms. The higher number of maps in the Rhythmia™ group despite a similar number of AT is explained by the convincing quality of the system, leading to more frequent map acquisition to more precisely elucidate AT features in case of uncertainty, or to better confirm the completeness of linear lesions.

Acute success rates were found similar for any system, leading to around 75% complete and 93% partial acute success in this highly selected population. Looking more in details however, procedural failure was noted more frequently with conventional 3D mapping systems (10 vs 5%), as were the undetermined AT mechanisms or precise locations which were twice more frequently observed using conventional 3D mapping systems, although the difference was of borderline significance possibly due to the low number of cases. This may possibly be related to the greater ability of the Rhythmia™ system to precisely delineate mechanisms and locations of an AT isthmus/focus. In the same way, there were significantly less diagnosis of focal and more diagnosis of macro-reentry mechanisms in patients investigated with the Rhythmia™ system compared to Carto/NavX™. This should not be interpreted by a hypothetical different population, but more likely by a more accurate in-depth determination of the actual AT mechanism [17]. In fact, more undetermined mechanisms were observed using standard 3D mapping systems. While entrainment mapping may characterize focal or reentrant mechanisms as well, this technique was marginally used here because of the risk of AT modification or interruption. Instead, we found that high definition mapping alone may depict AT mechanisms with enough precision, especially using the Rhythmia™ system.

In addition, we observed that ablation of AT using the high-density Rhythmia™ 3D mapping system was achieving a higher long-term success rate compared to standard 3D mapping systems. Of note that this was observed despite the lack of contact force ablation catheters in

the Rhythmia™ group, while such catheters are considered to achieve better long-term results [22] and were used in most patients investigated with standard 3D mapping systems. Moreover, there were more left AT in group 1 which are usually considered more challenging to localize and ablate, and group 1 patients represented our very first experience with the Rhyhmia™ system, while more solid knowledge and habit were present using the Carto™ or NavX™. Thus, these differences will surely increase while gaining expertise in Rhythmia™. Better understanding of the AT mechanisms and/or critical reentry isthmuses using the Rhythmia™ system probably led to more precisely targeted RF applications, and thus to a better long-term outcome, although this remains speculative.

**Limitations**

LVEF was lower in group 2 and previous AFib ablations were more frequent in group 1, but groups appear quite similar for other clinical relevant parameters. Although they may be suspected to favour one or the other group, these differences were indeed minor or of borderline significance and probably did not have relevant implications.

Although procedures were consecutive in each group and performed over the same time period, the findings of this retrospective study should need now confirmation in a prospective randomized trial. Detection of recurrences was not based on ambulatory recordings. However this was similar for both groups, and relapses of AT are usually symptomatic and/or persistent, thus regular clinical follow-up probably did not miss a relevant number of recurrent arrhythmias.

The high recurrence rates observed here reflect the selected population, since most of cases were redo procedures, or underwent previous surgery or AFib ablation. All these conditions are known to be related to more difficult procedures. Thus, our results should not be applicable to unselected AT ablation procedures. Moreover, attempts to reinduce AT or use of isoproterenol were not routinely performed after resumption of sinus rhythm by ablation, and this also may explain the high recurrence rate.

Use of contact force ablation catheters will probably still increase the long-term success rate in the Rhythmia™ group and render the differences more relevant.

This study was dedicated to AT, and whether ultra-high density mapping systems are useful for AFib or ventricular tachycardia ablation is not established. Although some publications tend to show that 3D mapping systems are equivalent for pulmonary vein isolation [23], a very recent study demonstrated the superiority of ultra high density mapping in AFib recurrences through detection of concealed low-voltage signals after pulmonary vein isolation [24].

No blanking period was used in this study, allowing to consider early recurrences as long-term failures (22 patients before 3 months). Adding a blanking period was not feasible in this retrospective study, since cardioversion was not performed in every case with early relapse. Although blanking periods are used for most studies about AFib ablation, this does not seem to be the case for ablation of AT.

## CONCLUSION

Ultra-high density mapping as provided by the Rhythmia™ system allows lower long-term recurrences after AT ablation compared to standard high-density 3D mapping, possibly because of a better comprehensive approach of AT mechanisms due to the higher precision of mapping.

**CONFLICTS OF INTEREST :** None except for SC who is employed by Boston Scientific

## REFERENCES


1. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NAM 3rd, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM (2016) 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 67:e27-e115

2. Veenhuyzen GD, Knecht S, O'Neill MD, Phil D, Wright M, Nault I, Weerasooriya R, Miyazaki S, Sacher F, Hocini M, Jaïs P, Haïssaguerre M (2009) Atrial tachycardias encountered during and after catheter ablation for atrial fibrillation: part I: classification, incidence, management. Pacing Clin Electrophysiol 32:393–398

3. Jaïs P, Shah DC, Haïssaguerre M, Hocini M, Peng JT, Takahashi A, Garrigue S, Le Métayer P, Clémenty J (2000) Mapping and ablation of left atrial flutters. Circulation 101:2928–2934

4. Coffey JO, d'Avila A, Dukkipati S, Danik SB, Gangireddy SR, Koruth JS, Miller MA, Sager SJ, Eggert CA, Reddy VY (2013) Catheter ablation of scar-related atypical atrial flutter. Europace 15:414–419

5. Nakagawa H, Shah N, Matsudaira K, Overholt E, Chandrasekaran K, Beckman KJ, Spector P, Calame JD, Rao A, Hasdemir C, Otomo K, Wang Z, Lazzara R, Jackman WM (2001) Characterization of reentrant circuit in macro reentrant right atrial tachycardia after surgical repair of congenital heart disease: isolated channels between scars allow “focal” ablation. Circulation 103:699–709

6. Sporton SC, Earley MJ, Nathan AW, Schilling RJ (2004) Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. J Cardiovasc Electrophysiol 15:310-315

7. Baker BM, Lindsay BD, Bromberg BI, Frazier DW, Cain ME, Smith JM (1996) Catheter ablation of clinical intra atrial reentrant tachycardias resulting from previous atrial surgery: localizing and transecting the critical isthmus. J Am Coll Cardiol 28:411–417

8. Akar JG, Kok LC, Haines DE, DiMarco JP, Mounsey JP (2001) Coexistence of type I atrial flutter and intra-atrial re-entrant tachycardia in patients with surgically corrected congenital heart disease. J Am Coll Cardiol 38:377–384

9. Triedman JK, Bergau DM, Saul JP, Epstein MR, Walsh EP (1997) Efficacy of radio frequency ablation for control of intra atrial reentrant tachycardia in patients with congenital heart disease. J am Coll Cardiol 30:1032–1038

10. Chan DP, Van Hare GF, Mackall JA, Carlson MD, Waldo AL (2000) Importance of atrial flutter isthmus in post operative intra-atrial reentrant tachycardia. Circulation 102:1283–1289

11. Ferrero de Loma-Osorio Á, Díaz-Infante E, Macías Gallego A; Spanish Catheter Ablation Registry Collaborators (2013) Spanish Catheter Ablation Registry. 12th Official Report of the Spanish Society of Cardiology Working Group on Electrophysiology and Arrhythmias (2012). Rev Esp Cardiol (Engl Ed) 66:983–992

12. Stevenson IH, Kistler PM, Spence SJ, Vohra JK, Sparks PB, Morton JB, Kalman JM (2005) Scar-related right atrial macro- reentrant tachycardia in patients without prior atrial surgery: electro anatomic characterization and ablation outcome. Heart Rhythm 2:594–601

13. Esato M, Hindricks G, Sommer P, Arya A, Gaspar T, Bode K, Bollmann A, Wetzel U, Hilbert S, Kircher S, Eitel C, Piorkowski C (2009) Color-coded threedimensional entrainment mapping for analysis and treatment of atrial macroreentrant tachycardia. Heart Rhythm 6:349–358

14. Huo Y, Schoenbauer R, Richter S, Rolf S, Sommer P, Arya A, Rastan A, Doll N, Mohr FW, Hindricks G, Piorkowski C, Gaspar T (2014) Atrial Arrhythmias Following Surgical AF Ablation: Electrophysiological Findings, Ablation Strategies, and Clinical Outcome. J Cardiovasc Electrophysiol 25:725–738

15. Nakagawa H, Ikeda A, Sharma T, Lazzara R, Jackman WM (2012) Rapid high resolution electroanatomical mapping: evaluation of a new system in a canine atrial linear lesion model. Circ Arrhythm Electrophysiol 5:417-424

16. Latcu DG, Bun SS, Viera F, Delassi T, El Jamili M, Al Amoura A, Saoudi N (2017) Selection of Critical Isthmus in Scar-Related Atrial Tachycardia Using a New Automated Ultrahigh Resolution Mapping System. Circ Arrhythm Electrophysiol 10:e004510

17. Anter E, McElderry TH, Contreras-Valdes FM, Li J, Tung P, Leshem E, Haffajee CI, Nakagawa H, Josephson ME (2016) Evaluation of a novel high-resolution mapping technology for ablation of recurrent scar-related atrial tachycardias. Heart Rhythm. 13:2048-2055

18. Nakagawa H, Ikeda A, Sharma T, Lazzara R, Jackman WM (2012) Rapid high resolution electroanatomical mapping: evaluation of a new system in a canine atrial linear lesion model. Circ Arrhythm Electrophysiol 5:417-424

19. Khongphatthanayothin A, Kosar E, Nademanee K (2000) Nonfluoroscopic three-dimensional mapping for arrhythmia ablation: tool or toy? J Cardiovasc Electrophysiol. 11:239-244

20. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot Nd, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA (2014) PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Can J Cardiol 30:e1-e63.

21. Bun SS, Delassi T, Latcu DG, El Jamili M, Ayari A, Errahmouni A, Berte B, Saoudi N (2018) A comparison between multipolar mapping and conventional mapping of atrial tachycardias in the context of atrial fibrillation ablation. Arch Cardiovasc Dis 111:33-40

22. Rottner L, Metzner A, Ouyang F, Heeger C, Hayashi K, Fink T, Lemes C, Mathew S, Maurer T, Reissmann B, Rexha E, Riedl J, Saguner AM, Santoro F, Kuck KH, Sohns C (2017) Direct Comparison of Point-by-Point and Rapid Ultra-High-Resolution Electroanatomical Mapping in Patients Scheduled for Ablation of Atrial Fibrillation. J Cardiovasc Electrophysiol 28:289-297

23. Lin H, Chen YH, Hou JW, Lu ZY, Xiang Y, Li YG (2017) Role of contact force-guided radiofrequency catheter ablation for treatment of atrial fibrillation: A systematic review and meta-analysis. J Cardiovasc Electrophysiol. 28:994-1005

24. Rottner L, Metzner A, Ouyang F, Heeger C, Hayashi K, Fink T, Lemes C, Mathew S, Maurer T, Reissmann B, Rexha E, Riedl J, Saguner AM, Santoro F, Kuck KH, Sohns C (2017) Direct Comparison of Point-by-Point and Rapid Ultra-High-Resolution Electroanatomical Mapping in Patients Scheduled for Ablation of Atrial Fibrillation. J Cardiovasc Electrophysiol 28:289-297

25. Segerson NM, Lynch B, Mozes J, Marks MM, Noonan DK, Gordon D, Jais P, Daccarett M (2018) High-density mapping and ablation of concealed low-voltage activity within pulmonary vein antra results in improved freedom from atrial fibrillation compared to pulmonary vein isolation alone. Heart Rhythm doi: 10.1016/j.hrthm.2018.04.035.

# Safety and acute results of ultra-high density mapping to guide catheter ablation of atrial arrhythmias in heart failure patients

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## ABSTRACT

***Aims:*** In heart failure (HF) patients, catheter ablation of atrial arrhythmias may have a significant impact on morbi-mortality. A novel ultra-high density mapping system (Rhythmia™, Boston Scientific, Marlborough, MA, USA) has been proposed to guide atrial ablation procedures. Patients with HF are likely to present challenging ablation and to be at higher risk of complications. We aimed to evaluate the safety of Rhythmia™-guided procedures in patients with HF.

***Methods:*** We retrospectively examined all Rhythmia™-guided procedures performed in Caen and Toulouse University Hospitals between 2015 and 2018 for atrial fibrillation and atrial tachycardia. Patients with a history of clinical HF or left ventricular ejection fraction (LVEF) <50% constituted the HF group.

***Results:*** During the study period, 296 procedures were conducted in 246 patients. The HF group comprised 170 procedures. Complications (tamponade, stroke, vascular or bleeding complications requiring surgical intervention or blood transfusion) occurred in 8 procedures (5.3%) in the HF group compared to 5 in the non-HF group (4.8%, p=1.000). There was no predictive factor of complications occurrence, despite a trend toward older age (p=0.051). Procedures in the HF group were longer, with longer fluoroscopy and mapping duration. Acute success was similar between groups, with 65.9% complete success in both groups. Patients with reduced LVEF (3.2%) did not experience more complications than those with HF and preserved ejection fraction (6.6%, p=0.469).

***Conclusion:*** Rhythmia™-guided procedures for complex atrial arrhythmias are safe in patients presenting with HF either with preserved or reduced LVEF, despite the longer mapping and procedure duration compared to control patients.

**KEYWORDS:** catheter ablation, heart failure, atrial arrhythmia, electroanatomic mapping system

## CONDENSED ABSTRACT

We retrospectively reviewed Rhythmia™-guided procedures performed in Caen and Toulouse Hospitals for atrial arrhythmias to evaluate the safety of these procedures in patients with heart failure. There were no more complications in the heart failure group despite the longer mapping and procedure duration compared to control patients.

## WHAT'S NEW?

- This is the first report of the novel ultra-high density mapping system clinical use to guide procedures for atrial arrhythmias in patients with heart failure, either with reduced or preserved left ventricular function, compared to control patients.
- Heart failure patients did not experience more complications compared to control patients.
- Left ventricular dysfunction <50% was not associated with more procedural complications.
- Mapping, fluoroscopy and procedure durations were longer in heart failure patients.
- Acute success rates of procedures were comparable in heart failure patients and in control patients.

## INTRODUCTION

Congestive heart failure (HF) and atrial fibrillation (AF), two major cardiovascular conditions, often coexist. AF occurrence worsens the functional prognosis of patients with HF regardless of whether the patients have preserved or reduced left ventricular ejection fraction (LVEF) and increases mortality. [1,2] Catheter ablation (CA) of AF in a setting of HF is safe and has proven effectiveness in improving functional status, quality of life, LVEF, [3–7] and mortality. [8] Nevertheless, these procedures can be challenging in HF patients with dilated atria, fibrosis, or mitral regurgitation, and many patients will experience recurrences and repeated ablations. Three-dimensional electroanatomic (3D) mapping systems have been proposed to improve the outcomes of CA procedures, from only pulmonary veins isolation (PVI) to atrial substrate modification and scar-related atrial tachycardias (AT). These systems allow reduction in fluoroscopy duration, but whether they are able to improve clinical outcomes of AF ablation remains uncertain. [9,10] Moreover, they are sometimes of limited help for very complex AT mechanisms, and CA procedures of AT guided with conventional 3D systems may present high recurrence rates. [11,12] Recently, a novel ultra-high-density (UHD) mapping system (Rhythmia™, Boston Scientific, Inc., Marlborough, MA, USA) using a dedicated 64-pole mini-basket catheter (IntellaMap Orion™, Boston Scientific) has been developed, enabling rapid and accurate mapping with low signal/noise ratio and limited need for additional manual editing. [13,14] Several studies have reported the ability of this system to elucidate complex arrhythmias, especially in case of previous failure of CA guided with other systems, [15,16] although it was shown to require longer procedure and fluoroscopy durations than other 3D systems. [17,18] Although there is a need for an accurate and helpful 3D mapping system to guide CA, procedure-related complications are also a matter of concern in HF patients. Since the procedures guided by the UHD system are long, and the basket catheter is also irrigated, one may question the safety of these procedures in frail patients with HF, and data are very limited in this setting. The aim of our study was to evaluate the safety and peri-procedural outcomes of Rhythmia™-guided ablation procedures for atrial arrhythmias, in patients presenting with HF compared to controls patients.

## METHODS

### *Study population*

We conducted a retrospective study including every consecutive ablation procedure of AF or AT using the Rhythmia™ system at both University Hospitals of Caen and Toulouse from August 2015 to April 2018. We considered de novo and redo procedures, paroxysmal and persistent AF and AT. We excluded AT displaying typical ECG pattern of atrial flutter.

Patients were stratified by HF status: patients with a previous history of congestive HF and/or an altered left ventricular ejection fraction (LVEF) (i.e. <50%) were designated the HF group, and the remaining patients constituted the non-HF group. HF history was defined as either hospitalization for HF, or clinical signs of HF requiring diuretics in ambulatory patients.

Subgroups were also defined by HF patients with reduced LVEF<50% (HFrEF) and those with preserved LVEF ≥50% (HFpEF).

### *Peri-procedural care*

All procedures were performed according to standard of care and current guidelines. Patients were under efficient stable oral anticoagulation for at least four weeks and uninterrupted, even the morning prior to ablation. Contrast cardiac computed tomography or transesophageal echocardiography was performed the day before the procedure to rule out intracardiac thrombus.

### *Procedural settings*

All patients underwent ablation under mild/deep assisted sedation or general anaesthesia with continuous monitoring of non-invasive blood pressure, oxygen saturation, electrocardiogram (ECG) and fluid balance. After venous femoral access, intravenous heparin was infused, targeting an activated clotting time (ACT) >300 s. ACT was tested every 30 min and additional heparin was applied if necessary.

A decapolar electrode catheter was placed in the coronary sinus to serve as a timing reference for mapping. Trans-septal puncture was performed through an 8.5 Fr sheath (Swartz, BRK puncture needle, St. Jude Medical, Saint Paul, MN, USA) under fluoroscopy with contrast agent injection to confirm left atrium position (Xenetix 300™, Guerbet, France) and transoesophageal echocardiography guidance when needed.

Electroanatomic mapping was completed using IntellaMap Orion™. Radiofrequency (RF) ablation was performed with either a standard 4-mm-tip irrigated catheter (Celsius Thermocool™, Biosense Webster; Blazer OI™, Boston Scientific), a magnetic 4-mm-tip irrigated catheters (IntellaNav OI™, Boston Scientific), or a contact force sensing 4-mm-tip irrigated catheters (Tacticath™, St. Jude Medical). PVI was achieved using a wide circular antral linear ablation. Additional RF applications including linear ablation and/or ablation of complex fractionated atrial electrograms (CFAE) for persistent AF were performed at the physician's discretion. For AT, ablation targeted the critical isthmus or the area of focal origin. RF power was 20-35 W with a flow rate of 17-30 ml/min and a maximum temperature of 43°C. Pulmonary veins entrance and exit blocks, as well as bidirectional blocks for linear lesions were confirmed by conventional pacing and/or activation mapping. At the end of the procedure, all catheters and sheaths were removed, and manual compression was performed before a bandage was applied. The patient was monitored in the recovery unit then discharged 24 to 48 hours later after clinical examination, ECG and transthoracic echocardiography.

***Follow-up and data collection***

All patients were scheduled for follow-up visits at one and three months after the procedure with clinical examination and ECG to diagnose late complications and AT/AF recurrences. Clinical, ECG, echocardiographic and procedural data were collected from the patients' medical files.

### *Clinical endpoints*

The primary endpoint was the safety of the ablation procedure and was defined as the combination of procedure-related deaths and complications, defined as tamponade, stroke, acute HF, cardiogenic shock, vascular or bleeding complications requiring surgical intervention or blood transfusion. The secondary outcomes were procedure and mapping characteristics, acute success of ablation, hospitalization duration, and in-hospital diuretics regimen modifications. Complete success was defined for paroxysmal AF as complete PVI and for persistent AF and AT, as resumption of sinus rhythm during ablation and elimination of all documented ATs. Intermediate success was defined for persistent AF as failure to restore sinus rhythm together with increased AF cycle length (>20%) and successful electrical cardioversion, and for AT, as successful ablation of the clinical AT but failure to treat subsequent ATs. Failure of the procedure was defined as inability to perform complete PVI, to ablate the clinical AT or as the absence of impact on AF cycle length (<20%).

### *Statistical analysis*

Categorical variables were expressed as numbers and percentages and compared using the Pearson Chi square test or Fisher's exact test as suitable. Continuous variables were expressed as the mean ± standard deviation if normally distributed, otherwise as median values with 1$^{st}$ and 3$^{rd}$ quartiles and compared using Student's t-test or non-parametric Mann-Whitney test as needed. Association between baseline characteristics and the occurrence of clinical event was evaluated by univariate analysis. Variables with p value ≤0.20 in the univariate analysis were introduced in the multivariate analysis using a binary logistic regression model with Wald's step-by-step method. Statistical significance was set at a two-tailed probability level of <0.05. All analyses were performed using IBM SPSS Statistics for Windows version 23.0 (released 2015, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

### *Ethics*

This retrospective study based on previous collected data complied with the Declaration of Helsinki and French ethics guidelines. This study was approved by the regional ethics committee and the French committee of informatics and civil liberties (CNIL, conformity agreement n°2204611). All patients provided written informed consent for intervention and received a non-opposition letter, as requested by French authorities for retrospective studies.

## RESULTS

### *Baseline characteristics*

During the study period, 723 AF/AT ablation procedures were performed in the two centres and the Rhythmia™ system was used in 305 of them. Nine procedures were excluded because of a lack of procedural data and/or lost to follow-up patients. Finally, 296 procedures conducted in 246 patients were analysed and 170 of them (57.4%) constituted the HF group. In the HF group, 74 were performed in patients with preserved LVEF (43.5%), and 94 (55.2%) in patients with reduced LVEF. Two procedures were excluded from subgroup analysis due to a lack of LVEF data (Figure 1).

The procedures were performed mostly in men (71.5%) with a median age of 64 years old (56-69). The clinical characteristics are detailed in Table 1. As expected, patients in the HF group had more comorbidities, more underlying cardiomyopathies and more HF medications. They were more symptomatic, with lower LVEF and more echocardiographic abnormalities. Arrhythmias were also unequally distributed between the groups (p=0.005). AT represented more than a half of the treated arrhythmias in both groups. One third of the HF patients had persistent AF, and only 6% of them presented paroxysmal AF. Conversely, paroxysmal and persistent AF were more balanced in the non-HF group, respectively 19.8% and 25.2%. About two thirds of the patients were referred for a repeated ablation irrespective of HF status. Patients with HF had more frequent history of previous ablation at other sites than pulmonary veins and cavotricuspid isthmus (p=0.04).

**Figure 1: Study flow chart**

AF: atrial fibrillation; AT: atrial tachycardia; CTI: cavotricuspid isthmus; HF: heart failure; HFpEF: HF with preserved left ventricular ejection fraction, HFrEF: HF with reduced left ventricular ejection fraction; SVT: supraventricular tachycardia

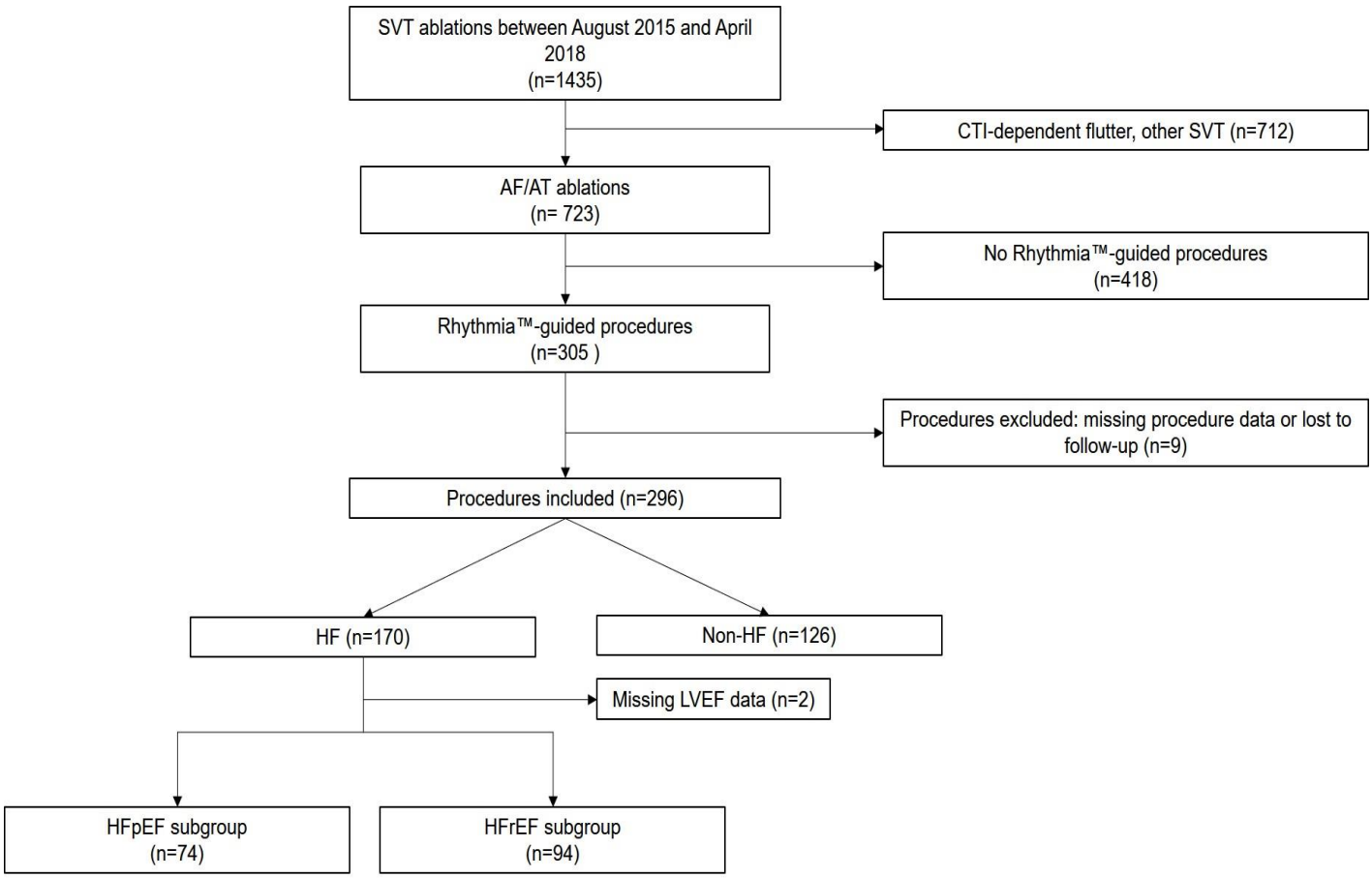


**Table 1. Baseline characteristics**

Continuous variables are reported as median with 1st and 3rd percentiles; categorical variables are reported as numbers and percentages. ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; AT: atrial tachycardia; CTI: cavotricuspid isthmus; CKD: chronic kidney disease (defined by estimated glomerular filtration <60 ml/min/1.73 m²); eGFR: estimated glomerular filtration; HF: heart failure; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor inhibitor; NYHA: New York Heart Association; PVI: pulmonary vein isolation

| | **Total** n=246 | **HF Group** n=135 | **No HF Group** n=111 | p |
|---|---|---|---|---|
| **Age** | 64 (56-69) | 65 (60-71) | 62 (53-69) | 0.015 |
| **Male gender** | 176 (71.5) | 97 (71.9) | 79 (71.2) | 0.906 |
| **Body mass index** | 27.6 (±4.9) | 28.1 (±5.1) | 27.1 (±4.8) | 0.150 |
| **Hypertension** | 135 (54.9) | 85 (63) | 50 (45) | 0.007 |
| **Diabetes mellitus** | 38 (15.4) | 29 (21.5) | 9 (8.1) | 0.004 |
| **Dyslipidaemia** | 96 (39) | 65 (48.1) | 31 (27.9) | 0.002 |
| **Cardiomyopathy** | | | | |
| none | 76 (30.9) | 0 (0) | 76 (68.5) | |
| Dilated | 76 (30.9) | 68 (50.4) | 8 (7.2) | |
| Ischemic | 35 (14.2) | 28 (20.7) | 7 (6.3) | <0.001 |
| Hypertrophic | 36 (14.6) | 27 (20.0) | 9 (8.1) | |
| Congenital | 22 (8.9) | 11 (8.1) | 11 (9.9) | |
| Transplant | 1 (0.4) | 1 (0.7) | 0 (0) | |
| **Stroke history** | 24 (9.8) | 21 (15.6) | 3 (2.8) | 0.001 |
| **Previous cardiac surgery** | 40 (16.3) | 23 (17.2) | 17 (15.3) | 0.732 |
| **NYHA class** | | | | |
| 1 | 68 (27.6) | 13 (9.6) | 55 (49.5) | |
| 2 | 120 (48.8) | 73 (54.1) | 47 (42.3) | <0.001 |
| 3 | 54 (22) | 45 (33.3) | 9 (8.1) | |
| 4 | 4 (1.6) | 4 (3) | 0 (0) | |
| **CHA2DS2-Vasc score** | | | | |
| 0 | 23 (11.8) | 3 (2.3) | 26 (23.9) | |
| 1 | 57 (23.2) | 19 (14.6) | 38 (34.9) | <0.001 |
| 2 | 52 (21.1) | 26 (20) | 26 (23.9) | |
| ≥3 | 101 (41.1) | 82 (63.1) | 19 (17.4) | |
| **eGFR** | 67.5 (±23) | 59.6 (±21.5) | 77.8 (±20.7) | <0.001 |
| **CKD** | 87 (35.4) | 67 (49.6) | 20 (18.0) | <0.001 |
| **Arrhythmia** | | | | |
| AT | 145 (58.9) | 84 (62.2) | 61 (55) | 0.005 |
| Paroxysmal AF | 30 (12.2) | 8 (5.9) | 22 (19.8) | |
| Persistent AF | 71 (28.9) | 43 (31.9) | 28 (25.2) | |
| **Redo procedure** | 146 (59.3) | 85 (63) | 61 (55) | 0.241 |
| **Previous ablation** | | | | |
| CTI | 134 (54.5) | 77 (57) | 57 (51.4) | 0.44 |
| PVI | 140 (56.9) | 81 (60) | 59 (53.2) | 0.302 |
| Other location | 120 (48.8) | 74 (54.8) | 46 (41.4) | 0.04 |

| | | | | |
|---|---|---|---|---|
| Surgical ablation | 8 (3.3) | 4 (3) | 4 (3.6) | 1 |
| **Echocardiography** | | | | |
| LVEF | 55 (45-60) | 45 (40-56) | 60 (59-65) | <0.001 |
| LVEF<50 | 72 (29.3) | 72 (53.3) | 0 (0) | <0.001 |
| Dilated left atrium | 153 (62.2) | 103 (76.3) | 50 (45) | <0.001 |
| Right dysfunction | 23 (9.3) | 20 (14.8) | 3 (2.7) | 0.003 |
| Mitral regurgitation | 29 (11.8) | 26 (19.2) | 3 (2.7) | <0.001 |
| **Cardiovascular medications** | | | | |
| Loop diuretics | 88 (35.8) | 85 (63) | 3 (2.7) | <0.001 |
| Thiazide diuretics | 29 (11.8) | 14 (10.4) | 15 (13.5) | 0.552 |
| MRA | 30 (12.2) | 28 (20.7) | 2 (1.8) | <0.001 |
| ACEI/ARB | 123 (50) | 86 (63.7) | 37 (33.3) | <0.001 |
| ARNi | 3 (1.2) | 3 (2.2) | 0 (0) | 0.25 |
| Beta-blockers | 162 (65.9) | 100 (74.1) | 62 (55.9) | 0.003 |
| Digoxin | 21 (8.5) | 14 (10.4) | 7 (6.3) | 0.36 |
| Antiplatelet agent | 31 (12.6) | 25 (18.5) | 6 (5.4) | 0.003 |
| **Antiarrhythmic drugs** | | | | |
| None | 93 (37.8) | 43 (31.9) | 50 (45) | <0.001 |
| Class Ic | 26 (10.6) | 6 (4.4) | 20 (18) | |
| Class III | 17 (6.9) | 9 (6.7) | 8 (7.2) | |
| Amiodarone | 110 (44.7) | 77 (57) | 33 (29.7) | |
| **Anticoagulation pre-ablation** | | | | |
| Vitamin K anticoagulant | 108 (43.9) | 75 (55.6) | 33 (29.7) | <0.001 |
| Direct oral anticoagulant | 131 (53.3) | 59 (43.7) | 72 (64.9) | |
| Heparin | 7 (2.8) | 1 (0.7) | 6 (5.4) | |
| **Oral anticoagulant interruption** | 17 (6.9) | 12 (8.9) | 5 (4.5) | 0.213 |
| **Device pre-ablation** | | | | |
| Pacemaker | 13 (5.3) | 11 (8.1) | 2 (1.8) | 0.04 |
| Implantable cardioverter defibrillator | 19 (7.7) | 17 (12.6) | 2 (1.8) | 0.001 |
| Cardiac resynchronization therapy | 8 (3.3) | 8 (5.9) | 0 (0) | 0.009 |

***Primary endpoint***

At three months, a total of 13 procedures (5.1%) met the primary endpoint of procedure-related deaths or complications. No patient died, and 14 complications occurred in 13 procedures with no difference between the groups: 8 procedures (5.3%) in the HF group had complications versus 5 in the non-HF group (4.8%) (p=1.000). The types of complications were balanced and equally distributed between groups: four tamponades occurred, two in each group (p=1); three groin bleedings , two in the HF group (p=1); four other vascular complications, either femoral arteriovenous fistula or pseudoaneurysms, two in each group (p=1); and three strokes, all in

the HF group (p=0.231). One HF patient experienced both femoral pseudoaneurysm requiring surgery, and a stroke. There was no hemodynamic, and no post-discharge complication. All the procedural outcomes are detailed in Table 2. Patients with complications had longer in-hospital stay (8 days, [5-13]) compared to those without complication (4 days, [3-4]) (p<0.001). The univariate analysis between procedures with and without complications did not report any predictor of complications occurrence. Patients with complications tended to be older (67 years [63.5-70.5] versus 63 years [55-69]), p=0.052), to have history of stroke more frequently (23.1% vs 9.3%, p=0.126), and to have more chronic kidney disease (53.8% versus 36.2%, p=0.242). Of note, complications occurrence was neither associated with HF group, nor LVEF impairment. In case of complications, fluroroscopy duration was longer (p=0.009), but there was a trend toward shorter RF duration (p=0.075). Univariate analysis of the primary endpoint is detailed in Table 3.

***Secondary endpoints***

All secondary outcomes are detailed in Table 2.

*Procedures and mapping data*

Procedures in the HF group were longer (p=0.01), with longer fluoroscopy duration (p<0.001), higher fluoroscopy dose (p<0.001), more maps (p=0.017), and longer mapping time (p<0.001), compared to procedures in the non-HF group. Conversely, the number of recorded electrograms (p=0.714), the RF duration (p=0.118), and the volume of infused serum (median 1.6 [1.2-2.4] litres, p=0.623) did not differ between the groups. PVI, CFAE, and cavotricuspid isthmus ablations were equally distributed between the groups. However, more linear lesions (p=0.028) and ablation at other locations (superior vena cava, coronary sinus, foci, p=0.016) were performed in case of HF. A total of 285 ATs were analysed, including those occurring during ablation of persistent AF. Most of them were macro-reentries (168/285, 58.9%) while the mechanism of 33 ATs remained undetermined (12.3%), with no difference between groups.

**Table 2. Procedural outcomes**

AF: atrial fibrillation; AT; atrial tachycardia; CFAE: complex fractionated atrial electrograms; CTI: cavotricuspid isthmus; EGM: electrograms; HF: heart failure; PVI: pulmonary veins isolation; RF: radiofrequency

| | **Total n=296** | **HF Group n=170** | **No HF Group n=126** | **p** |
|---|---|---|---|---|
| **Indication for ablation** | | | | |
| AT | 188 (63.5) | 114 (67.1) | 74 (58.7) | 0.001 |
| Paroxysmal AF | 28 (9.5) | 7 (4.1) | 21 (16.7) | |
| Persistent AF | 80 (27) | 49 (28.8) | 31 (24.6) | |
| **Procedures** | | | | |
| Duration. min | 210 (180-240) | 210 (180-240) | 180 (150-240) | 0.01 |
| RF Duration. min | 34 (19.8-54.9) | 29.5 (19.1-47.2) | 38 (21.5-60) | 0.118 |
| Fluoroscopy duration. min | 24 (14-43.5) | 31 (16-48) | 17.5 (11-32.5) | <0.001 |
| Fluoroscopy dose. Cgy/cm² | 3260 (1885-5989) | 4184 (2555-6707) | 2206 (1275-4538) | <0.001 |
| Fluid intake. litres | 1.6 (1.2-2.4) | 1.6 (1.2-2.1) | 1.7 (1.2-2.5) | 0.623 |
| Maps number | 4 (2-6) | 5 (3-6) | 4 (2-5) | 0.017 |
| Maps duration. min | 39.4 (25.8-54.6) | 45 (31-60.1) | 32.4 (22.9-49.5) | <0.001 |
| EGM | 34116 (20760-51162) | 34803 (19782-51162) | 32915 (21624-54696) | 0.714 |
| **Catheter type** | n=238 | n=135 | n=103 | |
| Standard | 187 (78.6) | 102 (75.6) | 85 (82.5) | 0.255 |
| Contact force | 35 (14.7) | 21 (15.6) | 14 (13.6) | |
| Magnetic | 12 (6.7) | 12 (8.9) | 4 (3.9) | |
| **Ablation** | | | | |
| PVI | 143 (48.3) | 81 (47.6) | 62 (49.2) | 0.935 |
| Linear | 220 (74.3) | 136 (80) | 84 (66.7) | 0.028 |
| CFAE | 78 (26.4) | 45 (26.5) | 33 (26.2) | 0.966 |
| CTI | 125 (42.2) | 74 (43.5) | 51 (40.5) | 0.719 |
| Other location | 71 (24) | 51 (30) | 20 (15.9) | 0.016 |
| **AT treated** | **n=285** | **n=189** | **n=96** | |
| Macro-reentry | 168 (58.9) | 109 (57.7) | 59 (61.5) | 0.611 |
| Micro-reentry | 41 (14.4) | 29 (15.3) | 12 (12.5) | 0.594 |
| Focal activation | 43 (15.1) | 30 (15.9) | 13 (13.5) | 0.727 |
| Unexplained | 35 (12.3) | 21 (11.1) | 12 (12.5) | 0.845 |
| **Acute ablation result** | | | | |
| Complete success | 195 (65.9) | 112 (65.9) | 83 (65.9) | 0.936 |
| Intermediate success | 95 (32.1) | 55 (32.3) | 40 (31.7) | |
| Failure | 6 (2.0) | 3 (1.8) | 3 (2.4) | |
| **Electric shock** | 64 (21.6) | 38 (22.4) | 26 (20.6) | 0.536 |
| **Hospitalization duration** | 4 (3-5) | 4 (3-5) | 3 (3-4) | <0.001 |
| **Diuretic increase** | 14 (4.8) | 12 (7.2) | 2 (1.6) | 0.028 |
| **Complicated procedures** | 13 (5.1) | 8 (5.3) | 5 (4.8) | 1.000 |
| Tamponade | 4 (1.4) | 2 (1.2) | 2 (1.6) | 1.000 |
| Bleeding | 3 (1.0) | 2 (1.2) | 1 (0.8) | 1.000 |
| Vascular | 4 (1.4) | 2 (1.2) | 2 (1.6) | 1.000 |
| Stroke | 3 (1.0) | 3 (1.8) | 0 (0) | 0.231 |

**Table 3: Univariate analysis of the primary endpoint**

AF: atrial fibrillation; AT: atrial tachycardia; CFAE: complex fractionated atrial electrograms; CKD: chronic kidney disease (defined by estimated glomerular filtration <60 ml/min/1.73 m²); LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PVI: pulmonary vein isolation; RF: radiofrequency

| | **No Complication** n=283 | **Complications** n=13 | **p** |
|---|---|---|---|
| **Age** | 63 (55-69) | 67 (63.5-70.5) | 0.052 |
| **Male gender** | 207 (73.1) | 10 (76.9) | 1.000 |
| **Body mass index** | 27.7±5.0 | 27.4±4.6 | 0.826 |
| **Heart failure group** | 162 (57.2) | 8 (61.5) | 0.785 |
| **Cardiomyopathy** | 202 (71.4) | 8 (61.5) | 0.533 |
| **NYHA class≥3** | 80 (28.3) | 2 (15.4) | 0.526 |
| **Hypertension** | 157 (55.5) | 9 (69.2) | 0.401 |
| **Diabetes mellitus** | 47 (16.6) | 3 (23.1) | 0.466 |
| **CKD** | 94 (36.2) | 7 (53.8) | 0.242 |
| **Stroke history** | 26 (9.3) | 3 (23.1) | 0.126 |
| **Arrhythmia** | | | |
| AT | 181 (64) | 7 (53.8) | |
| Paroxysmal AF | 27 (9.5) | 1 (7.7) | 0.629 |
| Persistent AF | 75 (26.5) | 5 (38.5) | |
| **Redo procedure** | 185 (65.4) | 10 (76.9) | 0.553 |
| **Echocardiography** | | | |
| LVEF | 55 (45-60) | 57 (48-61) | 0.771 |
| LVEF<50% | 91 (32.2) | 3 (23.1) | 0.761 |
| **Cardiovascular medications** | | | |
| loop diuretics | 106 (37.5) | 5 (38.5) | 1.000 |
| Vitamin K anticoagulant | 118 (41.7) | 7 (53.8) | 0.404 |
| Direct oral anticoagulant | 156 (55.1) | 6 (46.2) | 0.578 |
| Antiplatelet agent | 38 (13.4) | 1 (7.7 | 1.000 |
| **Ablation procedure** | | | |
| Duration. min | 210 (180-240) | 210 (165-255) | 0.974 |
| RF Duration. min | 34.5 (20-55) | 13.5 (12.9-NA) | 0.075 |
| Fluoroscopy duration. min | 22 (14-42) | 50.5 (33.5-62.8) | 0.009 |
| Fluoroscopy dose. Cgy/cm² | 3220 (1900-5950) | 3842 (1610-11201) | 0.496 |
| PVI | 136 (48.1) | 7 (53.8) | 0.780 |
| Linear | 209 (73.9) | 11 (84.6) | 0.526 |
| CFAE | 76 (26.9) | 2 (15.4) | 0.525 |
| Contact force catheter | 35 (12.2) | 1 (7.7) | 1.000 |
| Contact force or magnetic catheter | 49 (17.3) | 1 (7.7) | 0.468 |
| **Hospitalization duration** | 4 (3-4) | 8 (5-13) | <0.001 |

Data about catheter types were available for 238 procedures. The majority were performed with standard 4mm-tip irrigated catheters irrespective to HF group (p=0.255).

*Acute results of ablation*

65.9% of procedures (195/296) were considered as a complete success (Figure 2), 32.1% (95/296) were considered as an intermediate success, and 2% (6/296) were considered as a failure of ablation. There was no difference between the HF and the non-HF group in the acute results of ablation (p=0.936).

Hospitalization of HF patients was longer (4 days [3-5]) than those without HF (3 days [3-4], p<0.001). Moreover, they more often required initiation or increase of diuretics therapy than non-HF patients (12 versus 2, respectively; p=0.028).

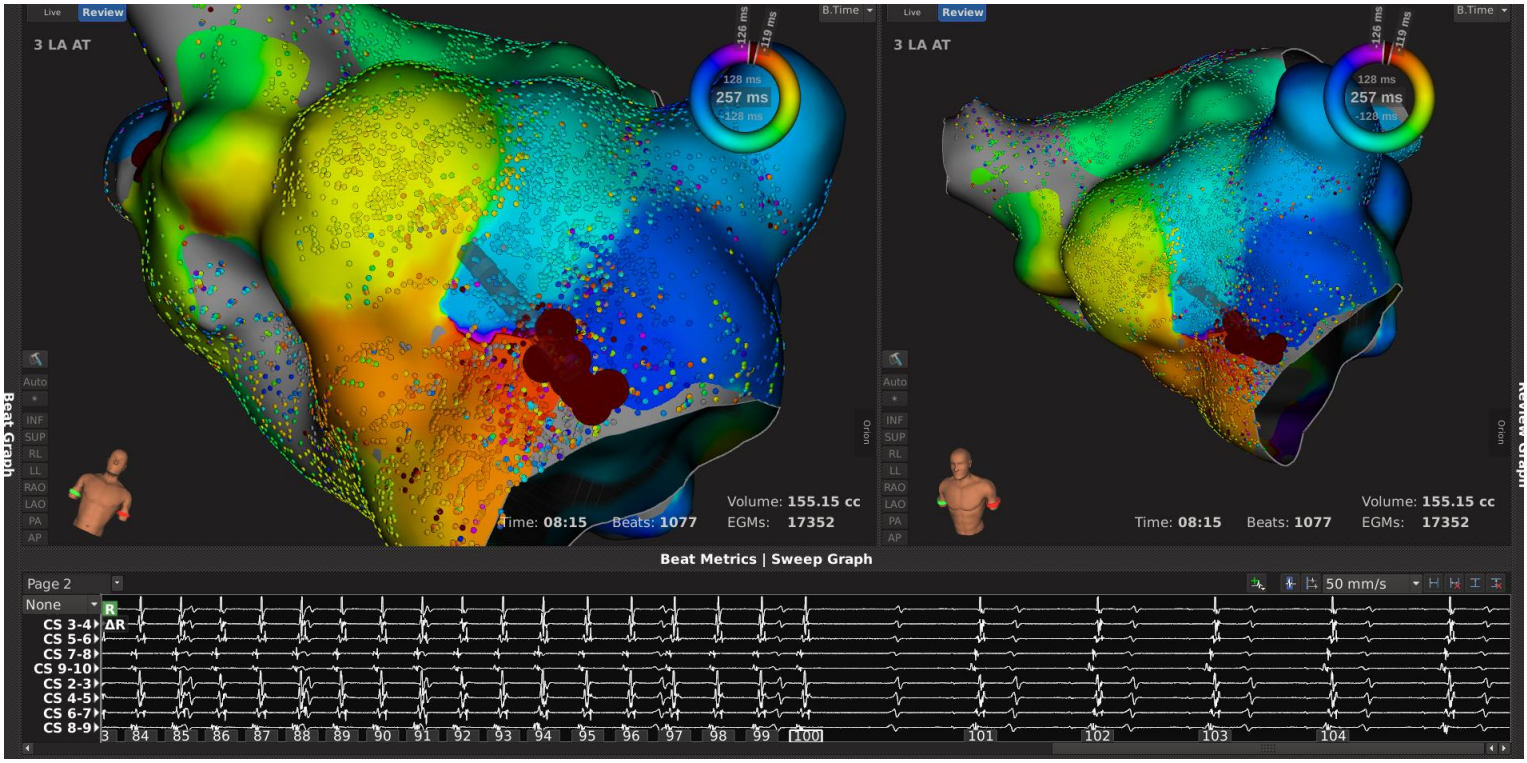
*Subgroup analysis: HFpEF versus HFrEF*

Patients with HFpEF and HFrEF were comparable in their baseline characteristics, comorbidities, symptoms, previous ablations, medications, and echocardiography findings except LVEF. The details of the patients' baseline characteristics are provided in supplemental table 1. Patients with HFrEF were more likely to be in persistent AF than those with HFpEF who presented more AT (p=0.052). Of note, patients with HFrEF had more dilated and ischemic cardiomyopathy, whereas those with HFpEF presented more hypertrophic cardiomyopathy (p<0.001). The latter carried more cardiac implanted devices.

There was no difference between the HFpEF and HFrEF groups in the primary endpoint of procedure-related complications (6.6% versus 3.2%, respectively; p=0.469). There was one tamponade in each group (p=1), one groin bleeding in each group (p=1), two surgical vascular complications in the HFpEF group (p=0.464), and two versus one stroke in the HFpEF and HFrEF group respectively (p=1). Procedural characteristics were also comparable, as were tachycardia mechanisms, lesions applied, and acute success. Patients with reduced LVEF had more CFAE ablation (p=0.049) and were more likely to need diuretics increase after ablation (p=0.013). The outcomes of the subgroups are detailed in supplemental table 2.

**Figure 2: Atrial tachycardia in a 67 years-old man with a previous history of persistent atrial fibrillation catheter ablation and ischemic cardiomyopathy with reduced ventricular function.**

Activation map showing critical isthmus on anterior wall, with sinus resumption during radiofrequency application at this site.




## DISCUSSION

This observational study is the first to evaluate the safety of the use of the novel UHD mapping system Rhythmia™ to guide CA of complex atrial arrythmias in patients with HF. The complications rates did not differ in patients with HF compared with controls, despite more comorbidities and longer procedures in the HF group. Moreover, the acute success of CA did not differ between the groups. Patients with reduced LVEF experienced no more complications than those with preserved LVEF.

AF occurrence is a well-known worsening factor of HF, increasing morbidity and mortality. Therefore, maintenance of sinus rhythm has long been a part of optimal HF patients' care, but it has no proven benefit with regard to survival and functional status when sinus rhythm was

maintained by drug therapy, probably due to the adverse effects of antiarrhythmic drugs. [19] Over the last two decades, CA has become an established, safe and effective treatment for symptomatic, drug-resistant AF in cases with normal cardiac function. Technical improvements, especially 3D mapping systems, allow higher rates of sinus rhythm restoration in complex arrhythmias. [20] More recent studies have shown various benefits of CA in patients with HF, including improvements of NYHA functional class, quality of life, and exercise capacity. [5–7] The CASTLE-AF study succeeded for the first time in proving the effectiveness of AF ablation in reducing mortality and worsening of HF. [8]

Complications rates were low in these studies, ranging from 2% to 9%. [5–8] A meta-analysis of randomized studies reported no increase in the risk of serious adverse events of AF ablation compared with medical therapy (RR=1.05; 95% CI: 0.96–1.16; p=0.30).[21] Of note, comparisons of CA between patients with HF and controls are scarce. In 2004, the Bordeaux group reported a direct comparison of 58 patients with HF and reduced LVEF <45% and 58 control patients matched for age, sex and AF type. They found no difference in the incidence of major complications (stroke and tamponade) between the groups (3% and 2%, respectively; p=0.74), but no mapping system was used. [3] Another study reported a higher rate of complications among patients with LVEF <40% (13%) compared to control patients (6%, p<0.01), after AF ablation guided by a 3D mapping system. [22] Previous studies of the Rhythmia™ system also reported a very low rate of complications (0-11%) [13–18] and were shown to be safe in particular populations such as paediatric patients [23] and patients with congenital heart disease. [24] However, we previously found that Rhythmia™-guided procedures for AT ablation were slightly longer than those guided by other 3D mapping systems, with no difference in the complications rates (1.7% in both groups), in non-selected patients regarding cardiac function. [17] This procedural length, combined with the need for irrigation of both the RF and basket catheters, could represent a potential issue in patients with HF, due to excessive fluid intake. Our present results could address this issue. Despite longer procedures with longer mapping duration than in the control group, there was no difference in median fluid intake and no acute congestive event in HF patients, even those with reduced LVEF. Our

present complications rates were similar with those previously reported in HF setting or with this particular mapping system. The TRUE-HD study, the largest prospective study assessing outcomes of this novel UHD mapping system, reported a 4% complications rate. [25]

Considering ablation characteristics, we also found that the patients in the HF group had a greater need of linear ablations. Previous studies of CA in HF patients compared to controls reported no difference in procedure/fluoroscopy duration and lesions applied but analysed only AF procedures. [3,22] Interestingly, ATs represented two-thirds of our HF group procedures, as expected, since many patients had redo ablations. Moreover, these ATs are frequently observed in HF patients and are complex to map and ablate, especially in cases with previously ablated dilated atria with large amounts of scar tissue. [26] In this challenging population, acute outcomes of CA were similar in HF and non-HF patients using the Rhythmia™ system. These results are encouraging with only 1.8% failure of ablation procedures in HF patients. Similar high acute success rates were previously reported for AF ablation procedures in HF patients by Hsu et al. [3] and Tondo et al. [22]

Within the HF group, we also examined the association between LVEF (<50% versus ≥50%) and clinical outcomes. Despite a few differences in pre-ablation characteristics with slightly more severe condition of patients in the HFrEF group, the procedural features and outcomes did not differ. Patients with HFrEF and patients in the HFpEF group experienced similar and low complication rates. As expected, the need for increase in diuretic intake after ablation was more frequent in case of HFrEF, but there was no difference in hospitalization duration. Our results are consistent with those reported by Black-Maier et al. that similarly compared AF ablation results and complications rates in patients with LVEF either <50 or ≥50% using standard 3D mapping systems (Carto™ or Ensite™). While this study did not include AT procedures, there were no difference between the two groups in major complications or procedural characteristics. [27]

### *Limitations*

Our study is retrospective, leading to possible confusion bias. Nevertheless, we included all consecutive procedures in each group over the same period of time. The choice of the Rhythmia™ system to guide ablation procedure was not randomized, and one could assume that our study population should be slightly different if all procedures were considered, regardless of the mapping system used. Conversely, our study population is probably representative of the real-life ablation landscape in a setting of HF, with repeated ablations and recurrent ATs. These are the most challenging and risky procedures because of procedural length and technical ablation issues, especially in case of HF. Finally, even in frail patients with complex arrhythmias, there was no higher complications rates when this novel UHD mapping system was used. LVEF was not determined by a core-lab but was retrieved from medical files. In addition, ablation lesions and AT mechanisms were not a priori defined but collected in ablation reports. Therefore, it would be important to address these biases and confirm our results in a prospective manner.

## CONCLUSION

The novel UHD mapping system Rhythmia™ is safe and helpful in achieving CA of atrial arrhythmias in patients presenting with HF, with either reduced or preserved LVEF. Considering both the positive outcome of sinus rhythm maintenance and the complexity of AF/AT ablation in these patients, it is important to be able to perform procedures using a highly accurate and safe mapping system.


## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

None declared.

**Supplemental table 1: Baseline characteristics of HF patients stratified by LVEF**

ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; AT: atrial tachycardia; CTI: cavotricuspid isthmus; CKD: chronic kidney disease (defined by estimated glomerular filtration <60 ml/min/1.73 m²); eGFR: estimated glomerular filtration; HFpEF: heart failure with preserved LVEF; HFrEF: heart failure with reduced LVEF; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor inhibitor; NYHA: New York Heart Association; PVI: pulmonary vein isolation

| | **HFpEF** n=62 | **HFrEF** n=72 | **p** |
|---|---|---|---|
| **Age** | 66 (60-69) | 65 (60-72) | 0.801 |
| **Male gender** | 41 (66.1) | 56 (77.8) | 0.175 |
| **Body mass index** | 28.3 (±5.1) | 27.7 (±5) | 0.508 |
| **Hypertension** | 45 (72.6) | 41 (56.9) | 0.155 |
| **Diabetes mellitus** | 11 (17.7) | 18 (25) | 0.401 |
| **Dyslipidaemia** | 29 (46.8) | 35 (48.6) | 0.864 |
| **Cardiomyopathy** | | | |
| None | 0 | 0 | |
| Dilated | 26 (41.9) | 42 (58.3) | |
| Ischemic | 9 (14.5) | 19 (26.4) | <0.001 |
| Hypertrophic | 21 (33.9) | 5 (6.9) | |
| Congenital | 6 (9.7) | 5 (6.9) | |
| Transplant | 0 (0) | 1 (1.4) | |
| **Stroke history** | 6 (9.7) | 14 (19.4) | 0.146 |
| **Previous cardiac surgery** | 11 (17.7) | 12 (16.7) | 1 |
| **NYHA class** | | | |
| 1 | 7 (11.3) | 6 (8.3) | |
| 2 | 36 (58.1) | 37 (51.4) | 0.268 |
| 3 | 19 (30.6) | 25 (34.7) | |
| 4 | 0 (0) | 4 (5.6) | |
| **CHA2DS2-Vasc score** | | | |
| 0 | 2 (3.2) | 1 (1.4) | |
| 1 | 8 (12.9) | 11 (15.3) | 0.194 |
| 2 | 16 (25.8) | 10 (13.9) | |
| ≥3 | 32 (51.6) | 49 (68) | |
| **eGFR** | 60.8 (±24.2) | 58.4 (±19.1) | 0.524 |
| **CKD** | 27 (43.5) | 40 (55.6) | 0.225 |
| **Arrhythmia** | | | |
| AT | 45 (72.6) | 39 (54.2) | |
| Paroxysmal AF | 4 (6.5) | 4 (5.6) | 0.052 |
| Persistent AF | 13 (21) | 29 (40.3) | |
| **Redo procedure** | 42 (67.7) | 42 (58.3) | 0.287 |
| **Previous ablation** | | | |
| CTI | 33 (53.2) | 43 (59.7) | 0.487 |
| PVI | 42 (67.7) | 38 (52.8) | 0.112 |

| | | | |
|---|---|---|---|
| Other location | 38 (61.3) | 35 (48.6) | 0.12 |
| Surgical ablation | 3 (4.8) | 1 (1.4) | 0.336 |
| **Echocardiography** | | | |
| LVEF | 58 (52-60) | 40 (30-45) | <0.001 |
| LVEF<50 | | | |
| Dilated left atrium | 50 (80.6) | 52 (72.2) | 0.505 |
| Right ventricle dysfunction | 6 (9.7) | 14 (19.4) | 0.143 |
| Mitral regurgitation | 12 (19.4) | 14 (19.4) | 1 |
| **Cardiovascular medications** | | | |
| Loop diuretics | 36 (58.1) | 48 (66.7) | 0.371 |
| Thiazide diuretics | 7 (11.3) | 6 (8.3) | 0.771 |
| MRA | 10 (16.1) | 18 (25.0) | 0.287 |
| ACEI/ARB | 37 (59.7) | 48 (66.7) | 0.473 |
| ARNi | 0 (0) | 3 (4.2) | 0.249 |
| Beta-blockers | 45 (72.6) | 54 (75) | 0.844 |
| Digoxin | 6 (9.7) | 8 (11.1) | 1 |
| Antiplatelet agent | 9 (14.5) | 16 (22.2) | 0.275 |
| **Antiarrhythmic drugs** | | | |
| None | 17 (27.4) | 26 (36.1) | |
| Class Ic | 4 (6.5) | 2 (2.8) | 0.146 |
| Class III | 7 (11.3) | 2 (2.8) | |
| Amiodarone | 34 (54.8) | 42 (58.3) | |
| **Anticoagulation pre-ablation** | | | |
| Vitamin K anticoagulant | 30 (48.4) | 44 (61.1) | 0.192 |
| Direct oral anticoagulant | 30 (50) | 28 (38.9) | |
| Heparin | 1 (1.6) | 0 (0) | |
| **Oral anticoagulant interruption** | 6 (9.7) | 6 (8.3) | 1 |
| **Device pre-ablation** | | | |
| Implantable cardioverter defibrillator | 1 (1.6) | 16 (22.2) | <0.001 |
| Cardiac resynchronization therapy | 0 (0) | 8 (11.1) | 0.007 |

**Supplemental table 2: Procedural outcomes in HF patients stratified by LVEF**

AF: atrial fibrillation; AT: atrial tachycardia; CFAE: complex fractionated atrial electrograms; CTI: cavotricuspid isthmus; EGM: electrograms; HFpEF: heart failure with preserved left ventricular ejection fraction; HFrEF: heart failure with reduced left ventricular ejection fraction; PVI: pulmonary vein isolation; RF: radiofrequency

| | **HFpEF n=74** | **HFrEF n=94** | **p** |
|---|---|---|---|
| **Indication for ablation** | | | |
| AT | 55 (74.3) | 57 (60.6) | 0.120 |
| Paroxysmal AF | 3 (4.1) | 4 (4.3) | |
| Persistent AF | 16 (21.6) | 33 (35.1) | |
| **Procedures** | | | |
| Duration. min | 180 (150-240) | 180 (150-240) | 0.371 |
| RF Duration. min | 41 (27-60) | 30 (20-60) | 0.412 |
| Fluoroscopy duration. min | 15 (12-18) | 13 (11-17) | 0.831 |
| Fluoroscopy dose. Cgy/cm² | 3200 (2190-3840) | 2550 (1560-4330) | 0.671 |
| Fluid intake. litres | 1.4 (1.18-2.5) | 1.7 (1.2-2) | 0.552 |
| Maps number | 2 (1-3) | 3 (2-5) | 0.657 |
| Maps duration. min | 33.5 (23.5-46) | 36 (22-46.6) | 0.798 |
| EGM | 24954 (14569-53305) | 32890 (20252-44140) | 0.523 |
| **Ablation** | | | |
| PVI | 37 (50) | 42 (44.7) | 0.535 |
| Linear | 61 (82.4) | 73 (77.7) | 0.874 |
| CFAE | 14 (18.9) | 29 (30.9) | 0.049 |
| CTI | 32 (43.2) | 40 (42.6) | 1.000 |
| Other location | 23 (31.1) | 28 (29.8) | 1.000 |
| **AT treated** | **n=90** | **n=98** | |
| Macro-reentry | 53 (58.9) | 56 (57.1) | 0.936 |
| Micro-reentry | 15 (16.7) | 14 (14.3) | 0.648 |
| Focal activation | 14 (15.5) | 16 (16.3) | 0.841 |
| Unexplained | 8 (8.9) | 12 (12.2) | 0.417 |
| **Acute ablation result** | | | |
| Complete success | 52 (70.3) | 59 (62.8) | |
| Intermediate success | 20 (27) | 32 (34) | 0.486 |
| Failure | 2 (2.7) | 1 (1.1) | |
| **Electric shock** | 17 (23) | 19 (20.2) | 0.850 |
| **Hospitalization duration** | 3 (3-3) | 3 (3-3) | 0.071 |
| **Diuretic increase** | 1 (1.4) | 11 (12) | 0.013 |
| **Complicated procedures** | 5 (6.6) | 3 (3.2) | 0.469 |
| Tamponade | 1 (1.4) | 1 (1.1) | 1.000 |
| Bleeding | 1 (1.4) | 1 (1.1) | 1.000 |
| Vascular | 2 (2.7) | 0 (0) | 0.464 |
| Stroke | 2 (2.7) | 1 (1.1) | 1.000 |

## REFERENCES


1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962.

2. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, *et al.* Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–5.

3. Hsu L-F, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, *et al.* Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004;**351**:2373–83.

4. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, *et al.* Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778–85.

5. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, *et al.* A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31–8.

6. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, *et al.* Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation* 2016;**133**:1637–44.

7. Vecchio N, Ripa L, Orosco A, Tomas L, Mondragón I, Acosta A, *et al.* Atrial Fibrillation in Heart Failure Patients with Preserved or Reduced Ejection Fraction. Prognostic significance of Rhythm control strategy with Catheter Ablation. *J Atr Fibrillation* 2019;**11**:2128.

8. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, *et al.* Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;**378**:417–27.

9. Estner HL, Deisenhofer I, Luik A, Ndrepepa G, Bary C von, Zrenner B, *et al.* Electrical isolation of pulmonary veins in patients with atrial fibrillation: reduction of fluoroscopy exposure and procedure duration by the use of a non-fluoroscopic navigation system (NavX). *Europace* 2006;**8**:583–7.

10. Bertaglia E, Bella PD, Tondo C, Proclemer A, Bottoni N, De Ponti R, *et al.* Image integration increases efficacy of paroxysmal atrial fibrillation catheter ablation: results from the CartoMerge Italian Registry. *Europace* 2009;**11**:1004–10.

11. Huo Y, Schoenbauer R, Richter S, Rolf S, Sommer P, Arya A, *et al.* Atrial arrhythmias following surgical AF ablation: electrophysiological findings, ablation strategies, and clinical outcome. *J Cardiovasc Electrophysiol* 2014;**25**:725–38.

12. Coffey JO, Avila A d', Dukkipati S, Danik SB, Gangireddy SR, Koruth JS, *et al.* Catheter ablation of scar-related atypical atrial flutter. *Europace* 2013;**15**:414–9.

13. Sohns C, Saguner AM, Lemes C, Santoro F, Mathew S, Heeger C, *et al.* First clinical experience using a novel high-resolution electroanatomical mapping system for left atrial ablation procedures. *Clin Res Cardiol* 2016;**105**:992–1002.

14. Schaeffer B, Hoffmann BA, Meyer C, Akbulak RÖ, Moser J, Jularic M, *et al.* Characterization, Mapping, and Ablation of Complex Atrial Tachycardia: Initial Experience With a Novel Method of Ultra High-Density 3D Mapping. *J Cardiovasc Electrophysiol* 2016;**27**:1139–50.

15. Anter E, McElderry TH, Contreras-Valdes FM, Li J, Tung P, Leshem E, *et al.* Evaluation of a novel high-resolution mapping technology for ablation of recurrent scar-related atrial tachycardias. *Heart Rhythm* 2016;**13**:2048–55.

16. Laţcu DG, Bun S-S, Viera F, Delassi T, El Jamili M, Al Amoura A, *et al.* Selection of Critical Isthmus in Scar-Related Atrial Tachycardia Using a New Automated Ultrahigh Resolution Mapping System. *Circ Arrhythm Electrophysiol* 2017;**10**.

17. Maury P, Champ-Rigot L, Rollin A, Mondoly P, Bongard V, Galinier M, *et al.* Comparison between novel and standard high-density 3D electro-anatomical mapping systems for ablation of atrial tachycardia. *Heart Vessels* 2019;**34**:801–8.

18. Kosiuk J, Hilbert S, John S, Bertagnolli L, Hindricks G, Bollmann A. Preliminary experience with high-density electroanatomical mapping for ablation of atrial fibrillation - Comparison of mini-basket and novel open irrigated magnetic ablation catheter in consecutive patients. *Int J Cardiol* 2017;**228**:401–5.

19. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–77.

20. Lo L-W, Chen S-A. Three-dimensional electroanatomic mapping systems in catheter ablation of atrial fibrillation. *Circ J* 2010;**74**:18–23.

21. Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Bachuwa G, *et al.* Catheter ablation of atrial fibrillation with heart failure: An updated meta-analysis of randomized trials. *Int J Cardiol* 2018;

22. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, *et al.* Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol* 2006;**29**:962–70.

23. Mori H, Muraji S, Sumitomo N, Kato R, Imamura T, Komori A, *et al.* Safety and accuracy of the Rhythmia mapping system in pediatric patients. *Heart Rhythm* 2019;**16**:388–94.

24. Ernst S, Cazzoli I, Guarguagli S. An initial experience of high-density mapping-guided ablation in a cohort of patients with adult congenital heart disease. *Europace* 2019;**21**:i43–53.

25. Hindricks G, Weiner S, McElderry T, Jaïs P, Maddox W, Garcia-Bolao JI, *et al.* Acute safety, effectiveness, and real-world clinical usage of ultra-high density mapping for ablation of cardiac arrhythmias: results of the TRUE HD study. *Europace* 2019;**21**:655–61.

26. Bamimore A, Mounsey P. Ablation of atrial tachycardia and atrial flutter in heart failure. *Heart Fail Clin* 2013;**9**:501–14.

27. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, *et al.* Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018;**15**:651–7.

# Long-term clinical outcomes after catheter ablation of atrial arrhythmias guided by ultra-high density mapping system in heart failure patients

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## ABSTRACT

**Background:** Catheter ablation of atrial fibrillation (AF) and/or atrial tachycardia (AT) in heart failure (HF) patients can provide improvement in symptoms, cardiac function and survival. These procedures are challenging with higher recurrence rates compared to patients with normal cardiac function.

**Objective:** We aimed to compare long term outcomes of AF/AT ablations guided by an ultra-high density mapping system between HF patients and controls. Primary endpoint was the one-year recurrence rate of AF/AT.

**Methods:** We retrospectively examined all Rhythmia™-guided procedures performed in Caen and Toulouse University Hospitals between 2015 and 2018 for AF/AT. Patients with a history of clinical HF or left ventricular ejection fraction (LVEF) <50% constituted the HF group.

**Results:** 246 patients were included, 135 in the HF group. At one-year, 71 patients had experienced AF/AT recurrences, with no difference between HF group (31.9%) versus non-HF group (25.2%), p=0.262. AF/AT recurrence rates were not different whether HF patients had preserved (37.1%) or reduced (26.4%) LVEF, p=0.196 and not modified by antiarrhythmic drug therapy. Recurrence rates after the index procedure were also similar between groups. In multivariate analysis, patients with mitral regurgitation (p=0.011), hypertrophic cardiomyopathy (p=0.011) and persistent AF (p=0.02) were at higher risk of recurrence. AF/AT recurrence was not significantly associated with HF hospitalization (p=0.078) and HF status was the only independent predictive factor of HF hospitalization (p=0.002). Patients in the HF group were more likely to improve their NYHA class and LVEF than others. However, AF/AT recurrence was associated with the absence of NYHA improvement in HF patients (p=0.028).

**Conclusion:** Clinical outcomes of AF/AT ablations guided by ultra-high-density mapping system appear similar in HF and non-HF patients. Patients with HF exhibit higher improvement of NYHA status and LVEF.

**KEYWORDS:** atrial arrhythmia, heart failure, catheter ablation, clinical outcomes, electroanatomic mapping system

## INTRODUCTION

Congestive heart failure (HF) and atrial fibrillation (AF), two major cardiovascular conditions, often coexist. Patients with HF usually have chronically elevated filling pressures, that favour left atrial enlargement and AF occurrence. Besides, AF worsens their functional capacity and increases mortality, regardless of whether they have preserved or reduced left ventricular ejection fraction (LVEF).[1,2] Catheter ablation (CA) of AF in a setting of HF with reduced LVEF (HFrEF) is safe, and has proven its ability to improve functional status, quality of life, LVEF,[3–5] and mortality.[6] Data regarding CA of complex atrial arrhythmias in case of HF with preserved LVEF (HFpEF) are limited but encouraging. [7,8] Nevertheless, these procedures can be challenging in HF patients, who are likely to experience more recurrences, and repeated ablations than individuals with normal cardiac function, despite the use of three-dimensional (3D) electroanatomic mapping systems. [7,9] Recently, a novel ultra-high-density (UHD) mapping system (Rhythmia™, Boston Scientific, Inc., Marlborough, MA, USA), using a dedicated 64-pole mini-basket catheter (IntellaMap Orion™, Boston Scientific) has been developed, enabling rapid and accurate mapping with low signal/noise ratio, and limited need for additional manual editing. Several studies have reported the ability of this system to elucidate complex arrhythmias. [10,11] However, data about clinical use in HF patients are scarce, and whether this UHD system could improve CA results in this particular population remains unknown. The aim of our study was to assess clinical outcomes after Rhythmia™-guided ablation procedures of complex atrial arrhythmias in patients with clinical HF, compared to controls.

## METHODS

### *Study population*

We conducted a retrospective study including every consecutive ablation procedure of AF or atrial tachycardia (AT) using the Rhythmia™ system at both University Hospitals of Caen and Toulouse from August 2015 to April 2018. We considered de novo and redo procedures,

paroxysmal and persistent AF, as well as AT. We excluded AT displaying typical ECG pattern of atrial flutter. Patients were stratified by HF status: patients with a previous history of congestive HF and/or an altered LVEF (i.e. <50%) were designated the HF group, and the remaining patients constituted the non-HF group. HF history was defined as either hospitalization for HF, or clinical signs of HF requiring diuretics in ambulatory patients. We performed a subgroup analysis within the HF group between patients with LVEF<50% (HFrEF) and those with LVEF ≥50% (HFpEF).

***Radiofrequency ablation procedure***

All procedures were performed according to standard of care and current guidelines. Patients were under efficient stable oral anticoagulation for at least four weeks with no interruption prior to ablation. Contrast cardiac computed tomography or transesophageal echocardiography was performed the day before the procedure to rule out intracardiac thrombus. All patients underwent ablation under mild or deep assisted sedation or general anaesthesia. After venous femoral access, intravenous heparin was infused targeting an activated clotting time (ACT) >300 s. ACT was tested every 30 min, and additional heparin was applied if necessary. Trans-septal puncture was performed by standard technique under fluoroscopy and transoesophageal echocardiography guidance when needed. Electroanatomic mapping was completed using IntellaMap Orion™. Radiofrequency (RF) ablation was performed with either a standard 4-mm-tip irrigated catheter (Celsius Thermocool™, Biosense Webster; Blazer OI™, Boston Scientific), a magnetic 4-mm-tip irrigated catheters (IntellaNav OI™, Boston Scientific), or with a contact force sensing 4-mm-tip irrigated catheters (Tacticath™, St. Jude Medical). PVI was achieved using a wide circular antral linear ablation. Additional RF applications including linear ablation and/or ablation of complex fractionated atrial electrograms (CFAE) for persistent AF were performed at the physician's discretion. For AT, ablation targeted the critical isthmus or the area of focal origin. Procedural settings were detailed previously, along with results on safety, and immediate outcomes of these procedures.

### *Follow-up and data collection*

All patients were scheduled for follow-up visit three months after the procedure and every six months with clinical examination. AF/AT recurrences were documented either by electrocardiogram or holter recordings. Patients with recurrences later than three months after the index procedure were considered for repeated ablation. We collected clinical, electrocardiographic, echocardiographic, and procedural data from medical files.

### *Clinical endpoints*

The primary endpoint was one-year recurrence of AF/AT. Secondary endpoints were: hospitalizations for HF at one year, death of any cause, cardiovascular death, New York Heart Association (NYHA) class and LVEF improvements.

### *Statistical analysis*

Categorical variables were expressed as numbers and percentages and compared using the Pearson Chi square test or Fisher's exact test as suitable. Continuous variables were expressed as mean ± standard deviation if normally distributed, otherwise as median ($1^{st}$ and $3^{rd}$ quartiles), and compared using Student's t-test or non-parametric Mann-Whitney test as needed. Association between baseline characteristics and the occurrence of clinical event was evaluated by univariate analysis. Variables with p value ≤0.20 in the univariate analysis were introduced in the multivariate analysis using a binary logistic regression model with Wald step-by-step method. The Kaplan–Meier method was used to generate actuarial survival curves for each group. Events were censored at the time of first occurrence. Differences in time-to-event distributions were evaluated by means of the log-rank test. Wald statistics and Cox regression results were presented with Hazar Ratio (HR) and 95% confidence interval (CI). Statistical significance was set at a two-tailed probability level of <0.05. All analyses were performed using IBM SPSS Statistics for Windows version 23.0 (released 2015, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

### *Ethics*

This retrospective study based on previous collected data complied with the Declaration of Helsinki and French ethics guidelines. This study was approved by the regional ethics committee and the French committee of informatics and civil liberties (CNIL, conformity agreement n°2204611). All patients provided written informed consent for intervention and received a non-opposition letter, as requested by French authorities for retrospective studies.

## RESULTS

### *Baseline characteristics*

During the study period, 644 patients underwent AF/AT ablation procedures in our two centres, and 253 of them were performed with the Rhythmia™ system. Seven patients were lost to follow-up. Finally, 246 patients were included, 135 of them (54.9%) constituted the HF group (See Figure 1 for the study flow chart). In the HF group, 62 patients had preserved LVEF (46.3%), and 72 (53.7%) had reduced LVEF. One patient was excluded from subgroup analysis due to missing LVEF data.

The procedures were performed mostly in men (71.5%) with a median age of 64 years old (56-69). The clinical characteristics are detailed in table 1. As expected, patients in the HF group had more comorbidities, more underlying cardiomyopathies and more HF medications. They were more symptomatic, with lower LVEF and more echocardiographic abnormalities. Arrhythmias were also unequally distributed between the groups (p=0.005). AT represented more than a half of the treated arrhythmias in both groups. One third of the HF patients had persistent AF, and only 6% of them presented paroxysmal AF. Conversely, paroxysmal and persistent AF were more balanced in the non-HF group, respectively 19.8% and 25.2%. The majority of the patients had already undergone a previous CA (59.3%), irrespective of HF status. Patients with HF had more frequent history of non-PVI and non cavotricuspid isthmus ablation (p=0.04).

**Figure 1: Study flow chart**

AF: atrial fibrillation; AT: atrial tachycardia; CTI: cavotricuspid isthmus; HF: heart failure; HFpEF: HF with preserved left ventricular ejection fraction, HFrEF: HF with reduced left ventricular ejection fraction; SVT: supraventricular tachycardia

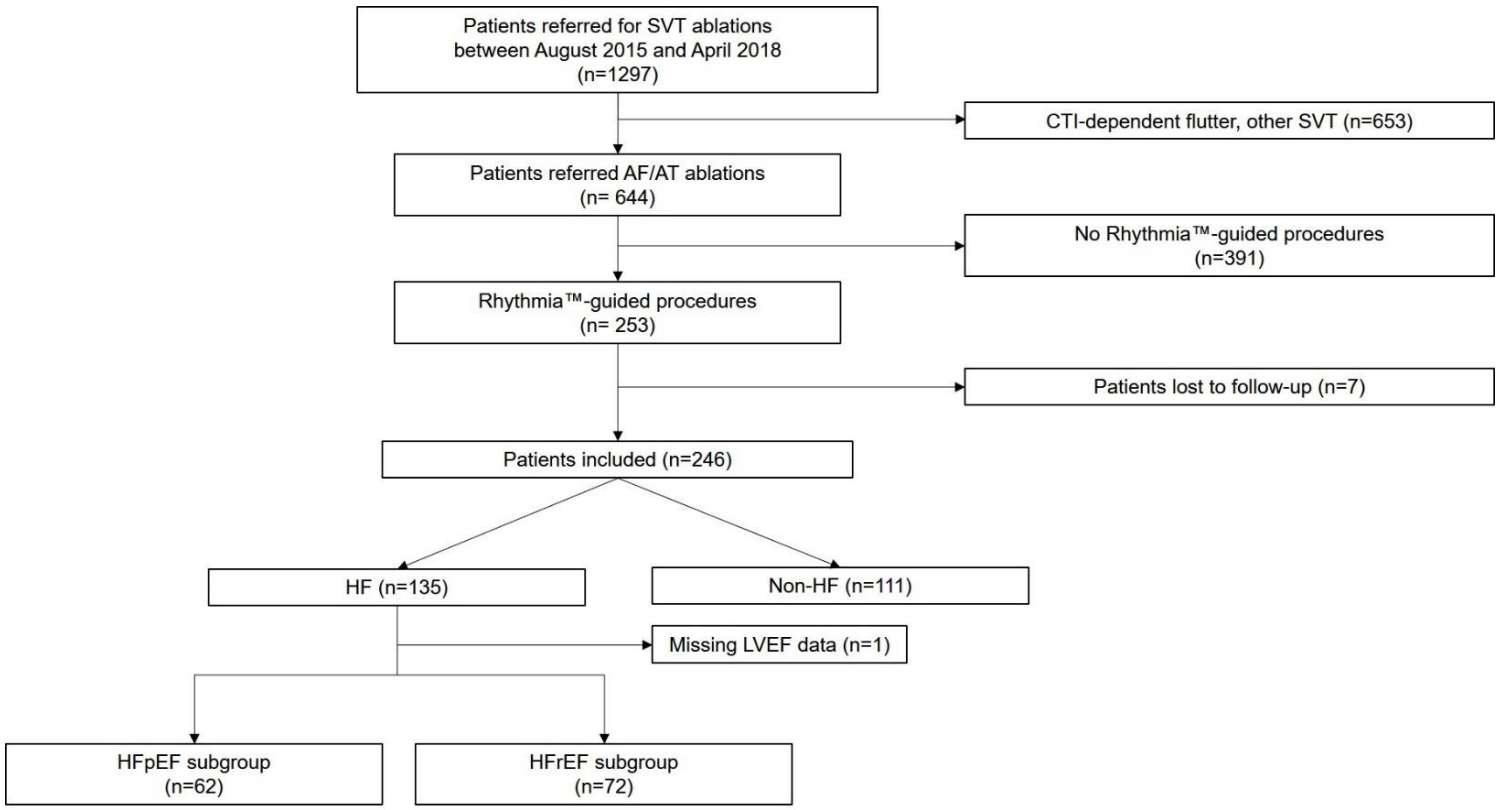

**Table 1. Baseline characteristics**

Continuous variables are expressed as mean (± standard deviation) or median ($1^{st}$ -$3^{rd}$ quartiles) as appropriate and categorical variables as numbers and percentages. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; CTI: cavotricuspid isthmus; CKD: chronic kidney disease (defined by eGFR <60 ml/min/1.73 m²); eGFR: estimated glomerular filtration; HF: heart failure; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor inhibitor; NYHA: New York Heart Association; PVI: pulmonary vein isolation

| | **Total** n=246 | **HF Group** n=135 | **No HF Group** n=111 | p |
|---|---|---|---|---|
| **Age** | 64 (56-69) | 65 (60-71) | 62 (53-69) | 0.015 |
| **Male gender** | 176 (71.5) | 97 (71.9) | 79 (71.2) | 0.906 |
| **Body mass index** | 27.6 (±4.9) | 28.1 (±5.1) | 27.1 (±4.8) | 0.150 |
| **Hypertension** | 135 (54.9) | 85 (63) | 50 (45) | 0.007 |
| **Diabetes mellitus** | 38 (15.4) | 29 (21.5) | 9 (8.1) | 0.004 |
| **Dyslipidaemia** | 96 (39) | 65 (48.1) | 31 (27.9) | 0.002 |
| **Cardiomyopathy** | | | | |
| none | 76 (30.9) | 0 (0) | 76 (68.5) | |
| Dilated | 76 (30.9) | 68 (50.4) | 8 (7.2) | |
| Ischemic | 35 (14.2) | 28 (20.7) | 7 (6.3) | <0.001 |
| Hypertrophic | 36 (14.6) | 27 (20.0) | 9 (8.1) | |
| Congenital | 22 (8.9) | 11 (8.1) | 11 (9.9) | |
| Transplant | 1 (0.4) | 1 (0.7) | 0 (0) | |
| **Stroke history** | 24 (9.8) | 21 (15.6) | 3 (2.8) | 0.001 |
| **Previous cardiac surgery** | 40 (16.3) | 23 (17.2) | 17 (15.3) | 0.732 |
| **NYHA class** | | | | |
| 1 | 68 (27.6) | 13 (9.6) | 55 (49.5) | |
| 2 | 120 (48.8) | 73 (54.1) | 47 (42.3) | <0.001 |
| 3 | 54 (22) | 45 (33.3) | 9 (8.1) | |
| 4 | 4 (1.6) | 4 (3) | 0 (0) | |
| **CHA2DS2-Vasc score** | | | | |
| 0 | 23 (11.8) | 3 (2.3) | 26 (23.9) | |
| 1 | 57 (23.2) | 19 (14.6) | 38 (34.9) | <0.001 |
| 2 | 52 (21.1) | 26 (20) | 26 (23.9) | |
| ≥3 | 101 (41.1) | 82 (63.1) | 19 (17.4) | |
| **eGFR** | 67.5 (±23) | 59.6 (±21.5) | 77.8 (±20.7) | <0.001 |
| **CKD** | 87 (35.4) | 67 (49.6) | 20 (18.0) | <0.001 |
| **Arrhythmia** | | | | |
| Atrial tachycardia | 145 (58.9) | 84 (62.2) | 61 (55) | 0.005 |
| Paroxysmal atrial fibrillation | 30 (12.2) | 8 (5.9) | 22 (19.8) | |
| Persistent atrial fibrillation | 71 (28.9) | 43 (31.9) | 28 (25.2) | |
| **Redo procedure** | 146 (59.3) | 85 (63) | 61 (55) | 0.241 |
| **Previous lesions** | | | | |
| CTI | 134 (54.5) | 77 (57) | 57 (51.4) | 0.44 |
| PVI | 140 (56.9) | 81 (60) | 59 (53.2) | 0.302 |
| Non-CTI/PVI lesions | 120 (48.8) | 74 (54.8) | 46 (41.4) | 0.04 |
| Surgical ablation | 8 (3.3) | 4 (3) | 4 (3.6) | 1 |
| **Echocardiography** | | | | |
| LVEF | 55 (45-60) | 45 (40-56) | 60 (59-65) | <0.001 |
| LVEF<50 | 72 (29.3) | 72 (53.3) | 0 (0) | <0.001 |
| Dilated left atrium | 153 (62.2) | 103 (76.3) | 50 (45) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Right dysfunction | 23 (9.3) | 20 (14.8) | 3 (2.7) | 0.003 |
| Mitral regurgitation | 29 (11.8) | 26 (19.2) | 3 (2.7) | <0.001 |
| **Cardiovascular medications** | | | | |
| Loop diuretics | 88 (35.8) | 85 (63) | 3 (2.7) | <0.001 |
| Thiazide diuretics | 29 (11.8) | 14 (10.4) | 15 (13.5) | 0.552 |
| MRA | 30 (12.2) | 28 (20.7) | 2 (1.8) | <0.001 |
| ACEI/ARB | 123 (50) | 86 (63.7) | 37 (33.3) | <0.001 |
| ARNi | 3 (1.2) | 3 (2.2) | 0 (0) | 0.25 |
| Beta-blockers | 162 (65.9) | 100 (74.1) | 62 (55.9) | 0.003 |
| Digoxin | 21 (8.5) | 14 (10.4) | 7 (6.3) | 0.36 |
| Antiplatelet agent | 31 (12.6) | 25 (18.5) | 6 (5.4) | 0.003 |
| **Antiarrhythmic drugs** | | | | |
| None | 93 (37.8) | 43 (31.9) | 50 (45) | |
| Class Ic | 26 (10.6) | 6 (4.4) | 20 (18) | <0.001 |
| Class III | 17 (6.9) | 9 (6.7) | 8 (7.2) | |
| Amiodarone | 110 (44.7) | 77 (57) | 33 (29.7) | |
| **Anticoagulation pre-ablation** | | | | |
| Vitamin K anticoagulant | 108 (43.9) | 75 (55.6) | 33 (29.7) | <0.001 |
| Direct oral anticoagulant | 131 (53.3) | 59 (43.7) | 72 (64.9) | |
| Heparin | 7 (2.8) | 1 (0.7) | 6 (5.4) | |
| **Oral anticoagulant interruption** | 17 (6.9) | 12 (8.9) | 5 (4.5) | 0.213 |
| **Device pre-ablation** | | | | |
| Pacemaker | 13 (5.3) | 11 (8.1) | 2 (1.8) | 0.04 |
| Implantable cardioverter defibrillator | 19 (7.7) | 17 (12.6) | 2 (1.8) | 0.001 |
| Cardiac resynchronization therapy | 8 (3.3) | 8 (5.9) | 0 (0) | 0.009 |

**Primary endpoint**

At one-year, 71 patients had experienced AF/AT recurrences with no difference between the groups: 43/135 HF patients relapsed (31.9%) versus 28/111 control patients (25.2%), p=0.262. The average rate of repeated ablation was 17.1%, with a trend toward a greater number of procedures performed in the HF group (1.2±0.5 procedures vs 1.1±0.4 respectively, p=0.065). Nevertheless, there was also no difference in recurrence rates between HF and non-HF groups after the index procedure (44.4% vs 36% respectively, p=0.196). In multivariate analysis using Cox regression, the cumulative risk of AF/AT recurrence was significantly higher in case of mitral regurgitation (HR=2.38, 95% CI 1.22 to 4.69, p=0.011), hypertrophic cardiomyopathy (HR=2.35, 95% CI 1.21 to 4.57, p=0.011), and persistent AF (HR=1.89, 95% CI 1.11 to 3.22, p=0.02). AF/AT recurrence rates were not significantly different, considering the type of ablation catheter used (36% with contact force catheters versus 47% with standard/magnetic catheters, p=0.277). One-year survival without AF/AT recurrence was not modified by

antiarrhythmic drug regimen, in both groups. Survival curves by the Kaplan Meier method are represented in Figure 2. Primary and secondary outcomes are detailed in Table 2.

**Figure 2: Kaplan Meier representation of outcomes**

Panel A: primary outcome of AF/AT recurrence; Panel B: AF/AT recurrence after index procedure; Panel C: AF/AT recurrence in non-HF group on/off antiarrhythmic drug therapy; Panel D: AF/AT recurrence in HF group on/off antiarrhythmic drug therapy
AAD: antiarrhythmic drug; AF: atrial fibrillation; AT: atrial tachycardia; HF: heart failure

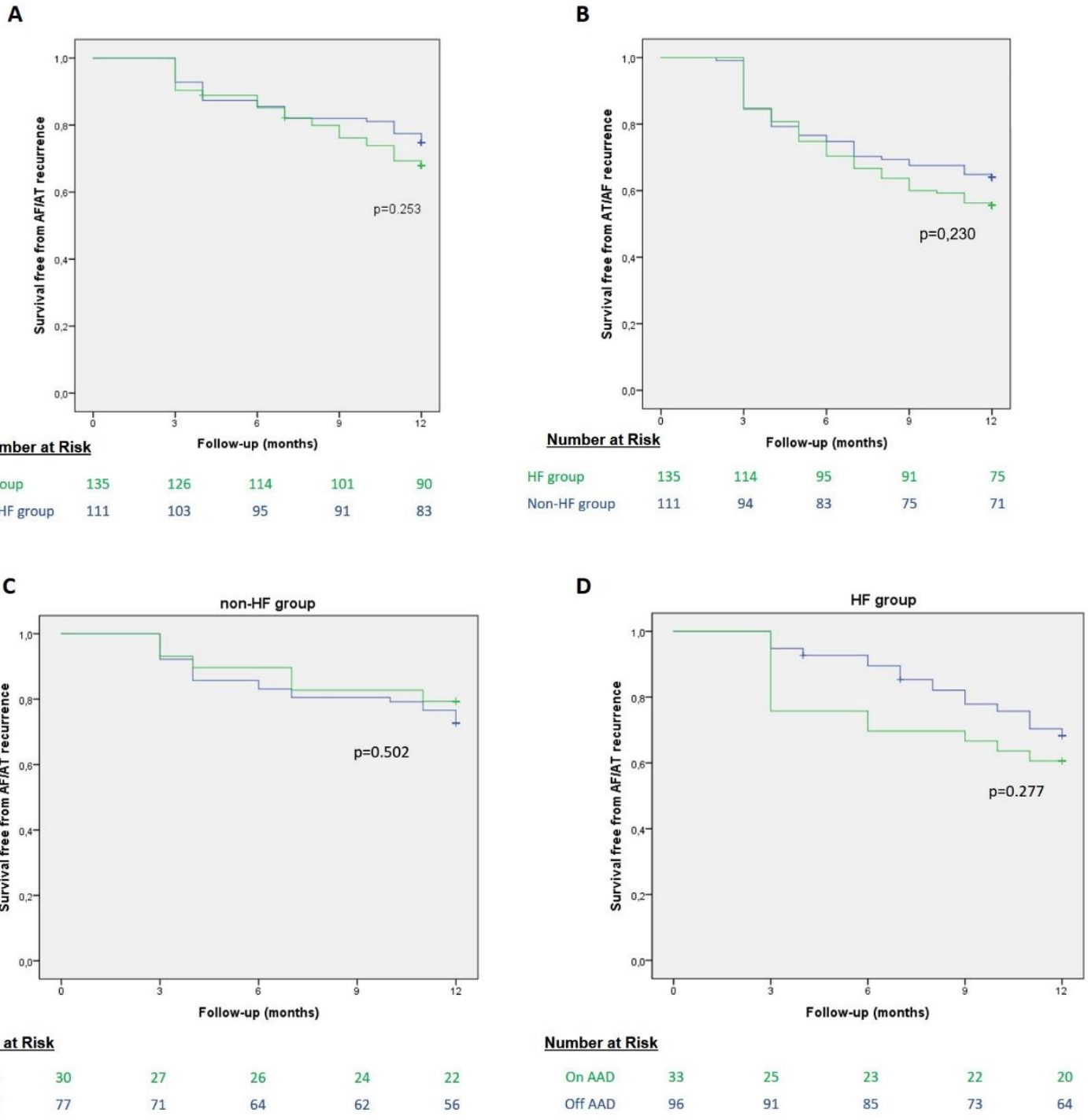

**Table 2: Clinical outcomes**

Continuous variables are expressed as mean (± standard deviation) or median ($1^{st}$ -$3^{rd}$ quartiles) as appropriate and categorical variables as numbers and percentages. AAD: anti-arrhythmic drug; AF: atrial fibrillation; AT: atrial tachycardia; HF: heart failure; HFpEF: HF with preserved LVEF; HFrEF: HF with reduced LVEF; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

| | **Total n=246** | **HF Group n=135** | **Non-HF Group n=111** | **p** | **HFpEF n=62** | **HFrEF n=72** | **p'** |
|---|---|---|---|---|---|---|---|
| **AF/AT recurrence** | 71 (28.9) | 43 (31.9) | 28 (25.2) | 0.262 | 23 (37.1) | 19 (26.4) | 0.196 |
| **AF/AT recurrence after one procedure** | 100 (40.6) | 60 (44.4) | 40 (36) | 0.194 | 30 (48.4) | 29 (40.3) | 0.386 |
| **N procedures** | 1.2 (±0.5) | 1.2 (±0.5) | 1.1 (±0.4) | 0.065 | 1.2 (±0.5) | 1.3 (±0.5)) | 0.341 |
| **AF/AT recurrence on AAD**, n=106 | 39 (36.8) | 23 (33.8) | 16 (42.1) | 0.409 | 13 (44.8) | 10 (25.6) | 0.124 |
| **AF/AT recurrence off AAD**, n=140 | 32 (22.9) | 20 (29.9) | 12 (16.4) | 0.071 | 10 (30.3) | 9 (27.3) | 1.000 |
| **AAD at one-year** | 106 (43.1) | 68 (50.4) | 38 (34.2) | 0.014 | 29 (46.8) | 39 (54.2) | 0.488 |
| **AAD termination** | 62 (26.4) | 33 (25.6) | 29 (27.4) | 0.768 | 21 (35.6) | 11 (15.9) | 0.014 |
| **Death** | 3 (1.2) | 3 (2.2) | 0 (0) | 0.254 | 0 (0) | 3 (4.2) | 0.249 |
| **Cardiovascular death** | 1 (0.4) | 1 (0.7) | 0 (0) | 1 | 0 (0) | 1 (1.4) | 1 |
| **HF hospitalization** | 21 (8.5) | 19 (14.1) | 2 (1.8) | <0.001 | 8 (12.9) | 11 (15.3) | 0.806 |
| **Final NYHA** | | | | | | | |
| 1 | 136 (55.3) | 52 (38.5) | 84 (75.6) | | 29 (46.7) | 23 (32) | |
| 2 | 97 (39.4) | 71 (52.6) | 26 (23.5) | | 28 (45.2) | 42 (58.3) | 0.213 |
| 3 | 12 (4.9) | 11 (8.2) | 1 (0.9) | <0.001 | 5 (8.1) | 6 (8.3) | |
| 4 | 1 (0.4) | 1 (0.7) | 0 (0) | | 0 (0) | 1 (1.4) | |
| **NYHA improvement** | 105 (43.9) | 69 (51.9) | 36 (34) | 0.006 | 34 (54.8) | 34 (48.6) | 0.49 |
| **Final LVEF** | 60 (50-60) | 55 (45-60) | 60 (59-65) | <0.001 | 60 (55-62) | 45 (35-50) | <0.001 |
| **LVEF improvement** | 63 (25.6) | 58 (42.9) | 5 (4.5) | <0.001 | 18 (29) | 40 (55.5) | 0.001 |

**Secondary outcomes**

*Mortality*

Three patients died during the follow-up, all from the HF group. Therefore, the one-year survival was 98.8% with no difference between groups (p=0.254). There was only one cardiovascular death resulting from cardiogenic shock during pulmonary sepsis. One of the two remaining patients died from a biliary tract cancer, and the other from haemorrhagic complications of liver cirrhosis.

*Heart failure hospitalizations*

As expected, more HF patients (19/135, 14.1%) were hospitalized for worsening of HF during the follow-up, compared to controls (2/111, 1.8%), p<0.001 (Figure 2). AF/AT recurrence tended to increase the risk of HF admissions (HR=2.71, 95% CI 0.90 to 8.20, p=0.078), but HF status was the only independent predictive factor in multivariate analysis (HR=10.2, 95% CI 2.29 to 10.43, p=0.002). Conversely, patients referred for redux procedure were significantly less hospitalized for HF worsening than patients who underwent first CA procedure (HR=0.32, 95% CI 0.12 to 0.82, p=0.018). Among HF patients, we did not find any specific predictive factor associated with HF hospitalizations.

*Functional status*

At the end of the follow-up, 69 HF patients had improved their NYHA status by one or more class (51.9%), compared to 36 non-HF patients (34%), p=0.006. Among HF patients, AF/AT recurrence was negatively associated with NYHA improvement (HR=0.42, 95% CI 0.19 to 0.91, p=0.028).

*Cardiac function*

At one-year, we observed LVEF improvement, by 5% or more, in 46.4% of the HF patients and in 5.7% of the control patients (p<0.001). Paroxysmal AF was negatively associated with LVEF improvement in HF patients (HR=0.08, 95% CI 0.01 to 0.79, p=0.030). HF patients who experienced AF/AT recurrence were less likely to improve their LVEF than individuals who remained in sinus rhythm, but with no statistical difference (35.7% vs 51.8% respectively, p=0.126).

*Subgroup analysis*

Patients with HFpEF (n=62) and HFrEF (n=72) were comparable in their baseline characteristics, comorbidities, symptoms, previous ablations, medications, and echocardiography findings except LVEF. Baseline characteristics of patients of the subgroup analysis are detailed in table 3. AF/AT recurrence rates were not different whether HF patients had preserved (37.1%) or reduced (26.4%) LVEF, p=0.196. However, patients in HFpEF subgroup (35.6%) had more antiarrhythmic drug therapy discontinuation than HFrEF patients (15.9%), p=0.014. At one-year, there was a greater proportion of LVEF improvement among patients with HFrEF (55.6%) compared to patients with HFpEF (29%, p=0.002), whereas NYHA improvement was not different between the subgroups (47.2% versus 54.8% respectively, p=0.49).

## Table 3. Baseline characteristics in subgroups

Continuous variables are expressed as mean (± standard deviation) or median (1st -3rd quartiles) as appropriate and categorical variables as numbers and percentages. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; CTI: cavotricuspid isthmus; CKD: chronic kidney disease (defined by eGFR <60 ml/min/1.73 m²); eGFR: estimated glomerular filtration; HF: heart failure; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor inhibitor; NYHA: New York Heart Association; PVI: pulmonary vein isolation

| | **HFpEF** n=62 | **HFrEF** n=72 | **p** |
|---|---|---|---|
| **Age** | 66 (60-69) | 65 (60-72) | 0.801 |
| **Male gender** | 41 (66.1) | 56 (77.8) | 0.175 |
| **Body mass index** | 28.3 (±5.1) | 27.7 (±5) | 0.508 |
| **Hypertension** | 45 (72.6) | 41 (56.9) | 0.155 |
| **Diabetes mellitus** | 11 (17.7) | 18 (25) | 0.401 |
| **Dyslipidaemia** | 29 (46.8) | 35 (48.6) | 0.864 |
| **Cardiomyopathy** | | | |
| None | 0 | 0 | |
| Dilated | 26 (41.9) | 42 (58.3) | |
| Ischemic | 9 (14.5) | 19 (26.4) | <0.001 |
| Hypertrophic | 21 (33.9) | 5 (6.9) | |
| Congenital | 6 (9.7) | 5 (6.9) | |
| Transplant | 0 (0) | 1 (1.4) | |
| **Stroke history** | 6 (9.7) | 14 (19.4) | 0.146 |
| **Previous cardiac surgery** | 11 (17.7) | 12 (16.7) | 1 |
| **NYHA class** | | | |
| 1 | 7 (11.3) | 6 (8.3) | |
| 2 | 36 (58.1) | 37 (51.4) | 0.268 |
| 3 | 19 (30.6) | 25 (34.7) | |
| 4 | 0 (0) | 4 (5.6) | |
| **CHA2DS2-Vasc score** | | | |
| 0 | 2 (3.2) | 1 (1.4) | |
| 1 | 8 (12.9) | 11 (15.3) | 0.194 |
| 2 | 16 (25.8) | 10 (13.9) | |
| ≥3 | 32 (51.6) | 49 (68) | |
| **eGFR** | 60.8 (±24.2) | 58.4 (±19.1) | 0.524 |
| **CKD** | 27 (43.5) | 40 (55.6) | 0.225 |
| **Arrhythmia** | | | |
| Atrial tachycardia | 45 (72.6) | 39 (54.2) | 0.052 |
| Paroxysmal atrial fibrillation | 4 (6.5) | 4 (5.6) | |
| Persistent atrial fibrillation | 13 (21) | 29 (40.3) | |
| **Redo procedure** | 42 (67.7) | 42 (58.3) | 0.287 |
| **Previous lesions** | | | |
| CTI | 33 (53.2) | 43 (59.7) | 0.487 |
| PVI | 42 (67.7) | 38 (52.8) | 0.112 |
| Non-CTI/PVI lesions | 38 (61.3) | 35 (48.6) | 0.12 |
| Surgical ablation | 3 (4.8) | 1 (1.4) | 0.336 |
| **Echocardiography** | | | |
| LVEF | 58 (52-60) | 40 (30-45) | <0.001 |
| LVEF<50 | | | |

| | | | |
|---|---|---|---|
| Dilated left atrium | 50 (80.6) | 52 (72.2) | 0.505 |
| Right ventricle dysfunction | 6 (9.7) | 14 (19.4) | 0.143 |
| Mitral regurgitation | 12 (19.4) | 14 (19.4) | 1 |
| **Cardiovascular medications** | | | |
| Loop diuretics | 36 (58.1) | 48 (66.7) | 0.371 |
| Thiazide diuretics | 7 (11.3) | 6 (8.3) | 0.771 |
| MRA | 10 (16.1) | 18 (25.0) | 0.287 |
| ACEI/ARB | 37 (59.7) | 48 (66.7) | 0.473 |
| ARNi | 0 (0) | 3 (4.2) | 0.249 |
| Beta-blockers | 45 (72.6) | 54 (75) | 0.844 |
| Digoxin | 6 (9.7) | 8 (11.1) | 1 |
| Antiplatelet agent | 9 (14.5) | 16 (22.2) | 0.275 |
| **Antiarrhythmic drugs** | | | |
| None | 17 (27.4) | 26 (36.1) | |
| Class Ic | 4 (6.5) | 2 (2.8) | 0.146 |
| Class III | 7 (11.3) | 2 (2.8) | |
| Amiodarone | 34 (54.8) | 42 (58.3) | |
| **Anticoagulation pre-ablation** | | | |
| Vitamin K anticoagulant | 30 (48.4) | 44 (61.1) | 0.192 |
| Direct oral anticoagulant | 30 (50) | 28 (38.9) | |
| Heparin | 1 (1.6) | 0 (0) | |
| **Oral anticoagulant interruption** | 6 (9.7) | 6 (8.3) | 1 |
| **Device pre-ablation** | | | |
| Implantable cardioverter defibrillator | 1 (1.6) | 16 (22.2) | <0.001 |
| Cardiac resynchronization therapy | 0 (0) | 8 (11.1) | 0.007 |

*Complications*

Fourteen complications occurred in 13 procedures (i.e. tamponade, stroke, or vascular/bleeding complication requiring surgical intervention or blood transfusion) with no difference between the groups: 8 procedures (5.3%) in the HF group had complications versus 5 in the non-HF group (4.8%) (p=1.000), with no difference whether LVEF was preserved or reduced. Detailed analyses of complications and acute procedural outcomes were conducted in a previous study.

## DISCUSSION

Our present study is the first to evaluate long-term clinical outcomes after AF/AT ablation procedures guided by UHD mapping system, in patients with clinical HF, either with preserved or reduced LVEF. We showed that recurrence rates after complex ablations were not higher in HF patients than in non-HF patients. There was no difference in the mortality rates, whereas

HF patients were more likely to be hospitalized for HF worsening during the follow-up. Nevertheless, CA was associated with greater NYHA and LVEF improvement in HF patients compared to controls.

CA of complex atrial arrhythmias has been shown to be safe and able to improve prognosis of patients with HF, particularly in case of HFrEF. Nevertheless, those patients are at high risk of recurrence, and reported rates varied from 27-73% after one procedure to 23-34% after repeated ablation on or off antiarrhythmic drug therapy. [4,7–9,12,13]. Data are more limited in HFpEF patients, but they also seem to benefit from CA, despite high recurrence rates. [7,8,14] HF has been identified as an independent risk factor for AF/AT recurrence in several reports that compared CA outcomes in patients with or without HF. [7,9,13] These lower success rates in HF could be related to different mechanisms: atrial enlargement and structural remodelling, due to chronic high filling-pressures and/or mitral regurgitation, that favour perpetuation of AF and a higher proportion of persistent AF; ischemia or the cardiomyopathy itself that can also alter atrial myocardium; but also patients' frailty, that can prevent from long-lasting procedures' completion. There were only few studies, that directly compared outcomes of CA of AF between HF and control patients. Chen et al reported 27% of AF recurrence in patients with systolic dysfunction after PVI, achieved without 3D mapping, whereas patients with normal cardiac function had only 13% of recurrence (p=0.03). [9] Using a standard 3D mapping system, Cha et al reported respectively 38%, 25% and 16% one-year recurrence in patients, whether they had systolic dysfunction, diastolic dysfunction, or normal cardiac function.[7] Furthermore, success rates of AF ablation were previously reported lower in patients with LVEF<50% compared to patients with LVEF>50%.[12] Black-Maier et al. recently published outcomes of CA of AF in both HFrEF and HFpEF patients with respectively 32.6% and 33.9% of recurrence (p=NS), but lower rates of repeated ablations than in our study. [14] Our present one-year recurrence rates were consistent with previous reports, even a little lower. Moreover, HF status was not a predictive factor of AF/AT recurrence, as well as the alteration of LVEF among HF patients. Yang et al. reported that the type of recurrence in patients with previous CA of AF

was depending on the degree of atrial remodelling. Patients with more dilated atria and lower left atrial bipolar voltage would rather have AF than AT recurrence, suggesting that HF patients are likely to relapse in AF. [15] Conversely, ATs were the most frequent arrhythmia in our study population in both groups, with a high proportion of repeated ablations. Previous AF ablation procedures can lead to additional atrial scars and subsequent complex ATs. In our study, the type of arrhythmia was not predictive of recurrence. This UHD mapping system was already reported to succeed in improving comprehension and ablation success of complex ATs. [16,17] In our study, we identified mitral regurgitation, hypertrophic cardiomyopathy and persistent AF as predictive factors of recurrences. A multicentre registry also highlighted higher recurrence rates in HF patients with persistent AF compared to controls, whereas the results of CA for paroxysmal AF were not different between HF patients and controls. [13] Data about CA in this setting are scarce, but a systematic review has already reported higher recurrence rates in patients with hypertrophic cardiomyopathy compared to controls. [18]

As expected, patients in the HF group were more likely to be hospitalized for HF worsening, however, we reported in previous analyses on procedural safety, that they did not experience more hemodynamic complications related to CA procedures than controls. The other important result of our present work is the beneficial effect of CA on both NYHA class and LVEF in patients with HF. In patients with HFrEF, CA of persistent AF, using a 3D mapping system, was already reported to improve LVEF, peak oxygen consumption, and Minnesota living with HF questionnaire score. [4] Another study reported better improvement in 6 minutes walking distance, Minnesota score and LVEF, after PVI compared to atrioventricular node ablation combined with cardiac resynchronization. [3] Moreover, the CASTLE-AF trial, reported a decrease in a composite endpoint of mortality and hospitalization for HF in the CA group compared to control group, in patients with HFrEF. [6] Another study conducted in patients with HFpEF, showed that only patients who maintained sinus rhythm had improvement in echographic parameters. [8] We also reported here, that AF/AT recurrence was associated with lower improvement in functional status and LVEF. Black-Maier et al reported similar effect of

CA on AF recurrence and NYHA improvement in both HFrEF and HFpEF groups, as we did, but they did not include AT in their analysis. They also showed a trend toward a greater improvement in NYHA class in patients with HFpEF that nearly reached statistical significance. [14] Likewise, our patients with HFrEF did not improve their NYHA class more than HFpEF patients, despite a significant larger increase in LVEF.

Larger studies should be conducted to address the potential benefit of this novel mapping system in complex arrhythmias management in case of HF and the relative benefit of CA in the particular population of HFpEF patients.

### Limitations

Our study was retrospective, leading to possible confusion bias. Nevertheless, we included all consecutive procedures in each group over the same period of time. The choice of the Rhythmia™ system to guide ablation procedure was not randomized, and one could assume that our study population should be slightly different if all procedures were considered, regardless of the mapping system used. LVEF was not determined by a core-lab but was retrieved from medical files. We did not use a standardized arrhythmia recurrence diagnostic protocol and patients with HFrEF had more implanted device allowing asymptomatic recurrence documentation. Therefore, it would be important to address these biases and confirm our results in a prospective manner. Conversely, our study population is probably representative of the real-life ablation landscape in a setting of HF, with repeated ablations and recurrent ATs.

## CONCLUSION

CA of complex atrial arrhythmias performed in patients with HF, either with preserved or reduced LVEF, and guided by a novel UHD system, is associated with similar rates of AF/AT recurrence, and achieved greater improvement in both NYHA class and LVEF, compared to

non-HF patients. Outcomes of CA were similar in HF patients with preserved or reduced LVEF.

patients.

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## REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al.: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37:2893–2962.

2. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ: Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003; 107:2920–2925.

3. Khan MN, Jaïs P, Cummings J, et al.: Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008; 359:1778–1785.

4. Hunter RJ, Berriman TJ, Diab I, et al.: A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014; 7:31–38.

5. Di Biase L, Mohanty P, Mohanty S, et al.: Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation 2016; 133:1637–1644.

6. Marrouche NF, Brachmann J, Andresen D, et al.: Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med 2018; 378:417–427.

7. Cha Y-M, Wokhlu A, Asirvatham SJ, et al.: Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. Circ Arrhythm Electrophysiol 2011; 4:724–732.

8. Machino-Ohtsuka T, Seo Y, Ishizu T, et al.: Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. J Am Coll Cardiol 2013; 62:1857–1865.

9. Chen MS, Marrouche NF, Khaykin Y, et al.: Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004; 43:1004–1009.

10. Sohns C, Saguner AM, Lemes C, et al.: First clinical experience using a novel high-resolution electroanatomical mapping system for left atrial ablation procedures. Clin Res Cardiol 2016; 105:992–1002.

11. Schaeffer B, Hoffmann BA, Meyer C, Akbulak RÖ, Moser J, Jularic M, Eickholt C, Nührich JM, Kuklik P, Willems S: Characterization, Mapping, and Ablation of Complex Atrial Tachycardia: Initial Experience With a Novel Method of Ultra High-Density 3D Mapping. J Cardiovasc Electrophysiol 2016; 27:1139–1150.

12. Lutomsky BA, Rostock T, Koops A, Steven D, Müllerleile K, Servatius H, Drewitz I, Ueberschär D, Plagemann T, Ventura R, Meinertz T, Willems S: Catheter ablation of paroxysmal atrial fibrillation improves cardiac function: a prospective study on the impact of atrial fibrillation ablation on left ventricular function assessed by magnetic resonance imaging. Europace 2008; 10:593–599.

13. Ullah W, Ling L-H, Prabhu S, et al.: Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. Europace 2016; 18:679–686.

14. Black-Maier E, Ren X, Steinberg BA, et al.: Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. Heart Rhythm 2018; 15:651–657.

15. Yang P-S, Park Y-A, Kim T-H, Uhm J-S, Joung B, Lee M-H, Pak H-N: Which patients recur as atrial tachycardia rather than atrial fibrillation after catheter ablation of atrial fibrillation? PLoS ONE 2017; 12:e0188326.

16. Takigawa M, Derval N, Frontera A, et al.: Revisiting anatomic macroreentrant tachycardia after atrial fibrillation ablation using ultrahigh-resolution mapping: Implications for ablation. Heart Rhythm 2018; 15:326–333.

17. Kitamura T, Martin R, Denis A, et al.: Characteristics of Single-Loop Macroreentrant Biatrial Tachycardia Diagnosed by Ultrahigh-Resolution Mapping System. Circ Arrhythm Electrophysiol 2018; 11:e005558.

18. Providencia R, Elliott P, Patel K, et al.: Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Heart 2016; 102:1533–1543.

## DISCUSSION

A travers les différents projets de recherche clinique qui constituent ce travail de thèse, nous avons cherché à apporter des éléments de réponse à certaines questions non résolues dans la prise en charge rythmologique des patients en situation d'IC.

Tout d'abord, nous nous sommes intéressés à l'IC-FEp qui est devenue une problématique quotidienne courante dans nos services de cardiologie. Comme nous l'avons précédemment abordé en introduction, un des principaux écueils dans la prise en charge de ces patients est l'absence de traitement médicamenteux spécifique efficace, en raison de multiples phénotypes cliniques rendant difficile l'élaboration d'une stratégie thérapeutique unique. Il apparaît donc important d'identifier ces phénotypes de patients, afin de leur proposer une prise en charge adaptée, basée sur le traitement des comorbidités associées. Une des pistes de développement serait de parvenir à anticiper l'apparition des signes d'IC chez les patients à risque. En effet, il existe une phase pré-clinique probablement de plusieurs années pendant laquelle la DD va s'aggraver progressivement. Elle se limite d'abord à une atteinte de la relaxation ventriculaire (grade 1), qui va s'accompagner par la suite d'une élévation des pressions de remplissage gauches d'abord modérée (grade 2), puis plus importante, associée à des anomalies avancées de la compliance du ventricule gauche et un profil restrictif (grade 3). L'élévation des pressions pulmonaires, secondaires à l'augmentation des pressions de remplissage gauches, mais également à des anomalies de la vascularisation pulmonaire liées à une dysfonction endothéliale et une rigidification artérielle, va participer à la dégradation de la tolérance à l'effort. (1) L'identification de la DD et sa quantification repose essentiellement sur l'échographie et plus particulièrement sur l'association de quatre paramètres : la moyenne du rapport de l'onde E du flux transmitral avec l'onde e' du doppler tissulaire à l'anneau mitral latéral et septal ; les vitesses de l'onde e' en doppler tissulaire ; la vitesse du flux de régurgitation tricuspide ; et le volume indexé de l'oreillette gauche. (2) Par ailleurs, les anomalies de la fonction diastolique sont fréquentes dans la population générale, en l'absence de cardiopathie ou d'IC avérée. Une étude de cohorte américaine, réalisée au sein d'un comté

du Minnesota, avait retrouvé une prévalence globale de 25% de DD tous grades confondus, 6% d'altération de la FEVG <50% et seulement 2% d'IC clinique. 5.6% des individus avaient une DD, de grade 2 ou 3, associée à une fonction systolique normale. Après contrôle des autres facteurs (âge, sexe, fonction systolique), la présence d'une DD, quelle que soit son grade était un facteur prédictif de mortalité toute cause (3) La même équipe a publié une nouvelle évaluation de la même cohorte réalisée quatre ans plus tard. Ils ont rapporté une augmentation de la prévalence de la DD tous grades confondus à 39,2% et une aggravation de la DD chez 23.4% des participants. L'âge >65 ans était prédictif de cette aggravation. Enfin, la survenue d'IC clinique au cours d'un suivi de six ans était corrélée à la présence d'une DD. (4) Ces observations sont cohérentes avec l'hypothèse d'une évolution progressive de la DD asymptomatique vers l'apparition d'une IC-FEp, et il apparaît donc intéressant de réussir à identifier ces patients à risque de développer une IC-FEp, parmi les nombreux individus présentant une altération de la fonction diastolique. C'est probablement le cas des patients cumulant des comorbidités associées à la présence de la DD, pouvant ainsi l'aggraver, ou favoriser d'autres phénomènes participant à l'installation d'un tableau d'IC-FEp.

C'est pourquoi, nous nous sommes intéressés au SAS dont la présence, comme nous l'avons déjà vu, est souvent associée à une altération de la fonction diastolique et qui, par différentes voies, activation sympathique, production de substances vasoconstrictrices comme l'endothéline, ou encore stress oxydatif, va également participer aux mécanismes de l'IC. L'étude du SAS comme cofacteur de nombreuses pathologies, notamment cardiovasculaires, est depuis quelques années en pleine explosion. Nous avons déjà évoqué son rôle dans l'IC, ce qui a amené les sociétés de cardiologie à en recommander la prise en charge dans le cadre du traitement de l'IC. Malheureusement, il est largement sous diagnostiqué car les symptômes sont peu spécifiques, parfois absents et la polysomnographie (PSG), examen diagnostique de référence, reste d'accès assez restreint. On estime que 80% des patients ayant un trouble ventilatoire du sommeil s'ignorent, et que la population diagnostiquée et prise en charge ne représente que « la partie émergée de l'iceberg ». (5) On distingue, selon le nombre de

signaux physiologiques enregistrés et les conditions de réalisation de l'enregistrement, quatre familles de systèmes d'enregistrement. Le type 1, la PSG au laboratoire du sommeil, avec au moins sept signaux enregistrés, est l'examen de référence, mais sa mise en œuvre nécessite de disposer de laboratoires du sommeil avec des techniciens spécialisés, d'où des listes d'attente importantes. Depuis de nombreuses années, les appareils portables de type 3, permettant d'enregistrer deux à quatre signaux, sont proposés pour permettre un diagnostic simplifié du SAS, pouvant être réalisé en milieu surveillé ou en ambulatoire. Ces examens sont appelés polygraphie ventilatoire (PV) ou respiratoire afin de les différencier des PSG. Si la performance diagnostique globale de ces systèmes de type 3 pour le dépistage est satisfaisante, ces derniers souffrent néanmoins d'une fréquente sous-estimation de l'IAH, par non reconnaissance des périodes de sommeil/éveil pendant l'enregistrement, ainsi que d'une perte d'informations ou encore de pannes techniques, surtout lorsque l'enregistrement est réalisé à domicile. (6) Une méta-analyse de 2014 confirmait la bonne performance diagnostique des systèmes portables de type 3, mais meilleure en milieu surveillé qu'à domicile, pour le diagnostic de SAS modéré à sévère chez des patients à forte probabilité pré-test (évaluation clinique préalable), sans comorbidité associée pouvant entraîner une confusion diagnostique (insuffisance respiratoire, maladie neuromusculaire, IC). (7) C'est d'ailleurs dans cette situation que les moniteurs de type 3 sont proposés dans les recommandations de la société américaine du sommeil. (8) En France, le remboursement des examens diagnostiques (PSG ou PV) est accordé, dès lors que le patient est symptomatique (somnolence diurne et trois autres symptômes évocateurs). L'examen doit, au minimum, enregistrer une oxymétrie, et un flux aérien nasobuccal sur une période nocturne d'au moins six heures. (9) D'autre part, des travaux anciens avaient déjà montré une prévalence très élevée du SAS chez des patients porteurs de PM, par ailleurs très peu symptomatiques et donc difficile à dépister par les questionnaires habituellement utilisés. (10) C'est pourquoi plusieurs sociétés ont développé des algorithmes de détection automatique embarqués dans leurs PM, afin de proposer un dépistage du SAS chez les individus nécessitant une stimulation cardiaque. Même si cela n'a pas été rapporté, les patients relevant d'une stimulation cardiaque

ont un profil qui en fait des « candidats idéaux » à la DD. Ils sont souvent âgés de plus de 65 ans, hypertendus ou porteurs d'une cardiopathie. C'est pour ces raisons, que nous nous sommes intéressés au dépistage du SAS dans une population de patients nécessitant un PM et sélectionnés sur la présence d'une DD échographique, en l'absence d'altération de la FEVG. Notre choix s'est porté sur l'algorithme appelé Sleep Apnea Monitoring (SAM) et développé tout d'abord par la société Ela Medical™, devenue par la suite Sorin CRM™, Livanova™ et depuis l'année dernière Microport Sorin™. La première publication sur sa performance diagnostique remontait à 2004 par Defaye et al. (11) Puis une nouvelle étude randomisée avait été publiée en 2014 par la même équipe sur une version améliorée de l'algorithme, celle actuellement disponible dans les PM de cette société. La DREAM Study mettait en évidence une bonne corrélation de l'index donné par le PM, le RDI, avec l'IAH de la PSG, dont la valeur seuil de 20 évènements par heure, était associée à une sensibilité de 88,9% (IC 95% 65,3 à 98,6) et une spécificité de 84,6% (IC 95% 54,6 à 98,1) pour la détection du SAS sévère, dans une population non sélectionnée de patients relevant d'un PM anti-bradycardique. (12)

S'agissant d'une étude prospective, nous avons passé plusieurs mois à élaborer le protocole de recherche et, dans le même temps, effectué une revue de la littérature sur le dépistage du SAS par les outils présents dans les différents PM afin d'étayer notre projet. Notre but était de confirmer la bonne performance du SAM pour le diagnostic du SAS sévère, voire modéré à sévère, dans cette population de patients avec une DD et appareillés d'un PM, afin de pouvoir à l'avenir « profiter » de cet appareillage pour dépister les patients à risque de développer une IC, et, si possible, faciliter leur suivi après traitement par PPC. Les autres objectifs étaient de décrire le SAS dans cette population et éventuellement en corréler la sévérité au grade de DD, mais aussi analyser les arythmies supraventriculaires et ventriculaires associées, notamment nocturnes, pouvant être réduites par le traitement du SAS. Enfin, nous avons voulu rechercher une association avec le taux d'aldostérone plasmatique, en raison des liens connus entre ces deux pathologies, et car il s'agit d'une thématique importante dans notre équipe de recherche.

Concernant le déroulement de cette étude, une des premières observations a été la difficulté de recrutement des patients. Compte-tenu des données de prévalence de la DD dans la population, (3,4) du nombre calculé de patients nécessaires, et de notre volume d'implantation, nous avions prévu un recrutement sur six à neuf mois, mais il aura fallu finalement plus de 24 mois pour l'achever. Tout d'abord, si une DD était observée chez environ 70% des patients de 75 ans, dans l'étude observationnelle menée au sein d'une cohorte américaine, nous avons mis en évidence une altération isolée de la fonction diastolique chez « seulement » 44% des patients évalués en échographie, lors du screening de l'étude. (3) De plus, une importante proportion de patients a refusé de se plier à la PV en milieu contrôlé. Nos patients étaient essentiellement des octogénaires, peu symptomatiques à en juger par leurs réponses aux questionnaires d'Epworth et de Berlin, et donc peu enclin à accepter de revenir au CHU pour une nuit d'enregistrement. Si cette situation a rendu plus difficile la complétion de l'étude, et peut y avoir inclus un certain biais de recrutement, elle nous a conforté dans l'idée qu'un système de détection automatisé du SAS pouvait être d'une grande aide pour explorer cette population particulière de patients, afin de ne proposer une PV de confirmation qu'aux patients ayant un RDI élevé.

Nous avons pu confirmer que le SAM était un bon outil de dépistage du SAS dans cette population de patients. Nous avions préféré la PV par moniteur portable réalisée au laboratoire du sommeil à la PSG, afin d'avoir un examen de référence fiable mais relativement simple et plus couramment utilisé dans notre centre pour la confirmation du SAS, étant données les difficultés d'accès à la PSG. Cependant, il est possible que ce choix de l'examen de référence soit à l'origine des résultats de performance diagnostique un peu moins bons qu'attendus à la vue des autres publications sur cet algorithme, ou sur celui proposé par une autre société. Le RDI, basé sur l'enregistrement d'une seule variable physiologique est probablement moins précis que l'IAH déduit de l'enregistrement de multiples signaux lors d'études du sommeil classiques, PV ou PSG. Cependant, il est probable que la possibilité de disposer des informations du RDI sur le long terme, corrélées à la charge en FA, est un atout du système,

compte tenu de la variabilité des anomalies polygraphiques d'une nuit à l'autre. Nous avons testé une valeur mensuelle moyenne, comme l'avaient déjà fait Aimé et al., mais sans parvenir à montrer une performance diagnostique supérieure à celle du RDI ponctuel. Par ailleurs, le PM propose à l'interrogation le pourcentage de nuits ayant un RDI supérieur à la valeur seuil recommandée par le constructeur. Nous n'avons pas testé cette donnée, mais il serait intéressant d'évaluer si la charge en anomalies de l'impédancemétrie est prédictive de la présence d'un SAS significatif, peut-être plus précisément que la valeur ponctuelle. De même, Moubarak et al. ont montré que le RDI était soumis à une importante variabilité, les patients ayant un pourcentage élevé de nuits avec un RDI >20 étant plus âgés et plus hypertendus que les autres, suggérant également l'intérêt de s'intéresser à une charge d'anomalies respiratoires nocturnes. (13)

Par ailleurs, même si notre groupe de patients appareillés était trop restreint pour en tirer des conclusions définitives, il est probable que le SAM peut aussi aider à surveiller les patients appareillés, en donnant également des renseignements sur l'observance thérapeutique grâce aux données quotidiennes. Même si ces patients sont peu symptomatiques et donc peu demandeurs d'examens supplémentaires, ils sont à risque d'évoluer vers une IC-FEp. L'apparition d'un SAS, mais aussi de troubles du rythme supraventriculaires, sont des éléments pouvant aggraver l'hémodynamique cardiaque, c'est pourquoi les dépister précocement et les traiter pourraient permettre de ralentir l'évolution vers l'IC. Depuis 2017, il est également proposé en France de traiter par PPC les patients présentant un SAS obstructif modéré (IAH ≥15) associé à des comorbidités cardiovasculaires telles que l'HTA résistante, la FA récidivante, l'IC à fonction systolique altérée ou préservée, et la maladie coronaire. C'est pour cette raison que nous avons également cherché une valeur seuil de RDI permettant de dépister le SAS modéré à sévère, afin de pouvoir adresser ces patients à risque cardiovasculaire pour un examen de référence et exclure le SAS chez ceux ayant un RDI faible.

Cette étude ne répond pas à toutes les questions, et il faudra d'autres travaux, pour mieux utiliser les données issues de cet algorithme, adapter les valeurs seuils de charge en RDI élevés au profil des patients, que ce soit pour le dépistage, le suivi des patients traités, la surveillance des arythmies. D'autres travaux ont déjà été publiés sur l'utilisation de ces algorithmes embarqués dans des DAI. (14,15) Il n'est évidemment pas question de remplacer les études de sommeil pour confirmer le diagnostic, évaluer la sévérité, le type de SAS, mais de disposer d'un outil automatisé, disponible dans les prothèses cardiaques implantées pour une indication spécifique, afin de mieux repérer les patients à risque, et améliorer la prise en charge de situations d'IC souvent complexes.

Pour poursuivre dans le domaine des dispositifs implantés, nous nous sommes penchés sur la prévention primaire de la MS rythmique au moyen du DAI dans l'IC-FEr. Nous avons rappelé dans l'introduction les études qui ont permis d'établir les recommandations en vigueur et les limites actuelles de cette thérapeutique, notamment en ce qui concerne la prédiction de la MS rythmique, et donc la sélection des patients devant bénéficier de ce dispositif. Le critère d'éligibilité basé sur l'altération de la FEVG <35% est reconnu depuis plus de 10 ans et n'a, jusqu'à aujourd'hui, jamais été remis en cause. Néanmoins plusieurs questions se posent : Y-a-t-il une modalité d'imagerie préférentielle pour la mesure de la FEVG ; la valeur de la FEVG requise est-elle la même selon la modalité utilisée ; enfin, quelles autres informations pourraient aider à la prise de décision ? L'IRM est désormais reconnue comme la technique de référence pour la mesure de la FEVG, (16) en raison d'une meilleure reproductibilité, et car elle est moins soumise à des approximations géométriques, notamment en cas de dilatation importante du VG. (17)

Cependant, les études de prévention primaire étaient basées sur des mesures échographiques et en pratique quotidienne l'utilisation de l'IRM cardiaque est encore limitée par son accès. De nombreux patients sont adressés à notre CHU pour une indication de prévention primaire basée sur une mesure échographique, et il est difficile de prévoir une IRM pour chaque patient pour une nouvelle mesure de la FEVG. Il serait donc important de préciser

la place de l'IRM dans l'évaluation pré-implantation des patients, faute de pouvoir faire de l'IRM un examen aussi accessible que l'échocardiographie. Doit-on évaluer par IRM les patients ayant une FEVG proche du seuil (par exemple entre 30 et 35%) ; ou au contraire ceux qui ont un ventricule gauche particulièrement remodelé car l'échographie est plus sujette à un biais de mesure dans ces situations ; faut-il l'envisager pour les patients dont les mesures échographiques sont variables d'un examen à l'autre par exemple en cas de mauvaise échogénicité ; ou dans certaines étiologies de cardiomyopathie ? De plus, il a été montré à plusieurs reprises, comme dans notre travail, que la valeur de la FEVG-IRM était inférieure à celle obtenue en échographie. (18,19) Cela pose donc logiquement la question de la valeur seuil de FEVG-IRM à considérer pour décider de l'implantation d'un DAI prophylactique : doit-elle tenir compte de cette différence moyenne et être inférieure à celle admise en échographie ? Plusieurs séries observationnelles ont rapporté que les patients ayant une FEVG <35% avec une des modalités, mais pas avec l'autre, étaient plutôt à faible risque rythmique. Dans le travail de Rijnierse et al, les patients ayant une FEVG-IRM ≤35% mais une FEVG-2D >35%, et implantés d'un DAI prophylactique, avaient reçu moins de thérapies appropriées que ceux ayant également une FEVG-2D ≤35% (2,1% versus 10,4% par an, p=0.02). (19) Inversement, Rayatzadeh et al ont montré dans leur série que les patients implantés en prévention primaire sur un critère de FEVG-2D ≤35%, mais dont la FEVG-IRM >35%, n'avaient reçu aucune thérapie appropriée. (20) La particularité de notre série par rapport aux deux précédentes, réside dans le fait que la décision d'implantation pouvait être basée sur l'une ou l'autre mesure. Nous n'avons pas retrouvé de différence sur la survenue d'évènements, décès ou thérapies appropriées, entre ces patients et le reste de la population, mais notre taux de « mismatch » était bien moins important, il était de 10% chez nous contre 20 à 25 % dans ces deux séries. De ce fait, le très faible effectif de ce sous-groupe de patients ne permet aucune conclusion. Il est néanmoins probable que ces patients avec une FEVG limite, qui les amène à pouvoir être reclassés en fonction de la méthode de mesure, sont moins à risque que ceux ayant des FEVG plus altérées. Il ne faut pas oublier que, si le critère d'inclusion dans les essais de prévention primaire était une FEVG ≤30-35%, la FEVG moyenne

des patients inclus dans ces études était finalement entre 20 et 25%, et qu'aucune étude ne s'est spécifiquement penchée sur ces patients ayant une FEVG moins altérée, entre 31 et 35%. (21–24) Le but de notre travail n'était pas de montrer la supériorité d'une modalité d'examen sur l'autre, mais de chercher, d'une part, si la meilleure reproductibilité des mesures IRM permettait à la FEVG-IRM d'être mieux corrélée aux évènements, d'autre part, trouver la valeur de FEVG permettant de sélectionner les patients les plus à risque, et enfin, si les données de RT permettaient d'améliorer cette prédiction d'évènements. Finalement, nous avons bien mis en évidence une valeur seuil de FEVG-IRM plus basse et mieux corrélée à la survie sans évènement que la FEVG-2D. La FEVG-IRM permettait également de prédire la survenue de décès et de thérapies appropriées alors que le FEVG-2D n'était corrélée qu'aux thérapies appropriées. Nous avons également montré que l'association du RT et de la FEVG-IRM était plus fortement associée à la survenue d'un évènement, avec un risque relatif de 2,58 (IC 95% 1,54 à 4.30, p<0,001). Ces résultats semblent montrer dans notre population, en tenant compte des limites exposées dans les résultats, que l'altération sévère de la FEVG-IRM est plus étroitement liée à la survenue d'évènements, et que la possibilité d'y associer l'étude du RT renforce l'intérêt de l'IRM pour l'évaluation des candidats à la prévention primaire.

Les individus appareillés d'un DAI qui avaient une FEVG-IRM <22%, sont plus décédés et ont aussi reçu plus de thérapies appropriées, que ceux qui avaient une FEVG-IRM entre 22 et 35%, mais seuls 10 des 46 patients décédés (22%) avaient reçu des thérapies au cours du suivi précédant le décès. Dans les études, les thérapies appropriées sont souvent considérées comme un équivalent de mortalité rythmique, évitée par le DAI. Nous n'avions pas revu les causes de décès des 36 patients restants mais on peut imaginer qu'ils sont décédés d'aggravation de l'IC ou de causes non cardiaques. Ces patients ont-t-ils tiré un bénéfice de l'implantation d'un DAI prophylactique, ce n'est pas certain. D'un autre côté, les patients ayant une FEVG-IRM ≥22% ont reçu moins de thérapies et sont moins décédés, ce qui en fait des patients moins à risque d'évènements, rythmiques ou non rythmiques. Il n'est pas non plus évident que ces patients aient bénéficié de la pose d'un DAI. Nous avions déjà évoqué dans

l'introduction le fait que, finalement, une assez faible proportion des MS rythmiques survenait chez des patients ayant une FEVG altérée. Cependant, parmi ces derniers, il semblerait quand même cela soit les patients ayant une altération sévère de la FEVG qui tireraient le plus bénéfice d'un DAI prophylactique, même si on sait qu'une proportion non négligeable décédera d'une cause non rythmique. D'autre part, sur le plan médicamenteux, la prévention de la MS rythmique n'a pas fait beaucoup de progrès. La seule molécule utilisable dans l'IC reste aujourd'hui l'amiodarone, bien que de nouvelles molécules semblent avoir des effets prometteurs et sont en cours d'étude comme la ranolazine et l'azimilide. (25) Cependant, l'association sacubitril-valsartan, dernière molécule entrée dans la stratégie thérapeutique de l'IC-FEr, semble avoir également un effet sur la prévention de la MS rythmique. L'étude des modes de décès des patients de l'étude PARADIGM-HF avait montré que le traitement par LCZ696 permettait une réduction significative de la mortalité par progression de l'IC, mais aussi de la mortalité subite (HR 0,80, IC 95% 0,68 à 0,94, p=0,008). (26) Un autre travail, réalisé chez des patients tous implantés d'un DAI et traités successivement par IEC/ARAII puis par LCZ696, a rapporté une réduction des tachycardies ventriculaires non soutenues, des épisodes soutenus, des chocs appropriés mais aussi des extrasystoles ventriculaires avec une amélioration du pourcentage de stimulation biventriculaire chez les patients équipés d'un DAI-RC. (27) Compte-tenu de la morbimortalité et du coût associés à la prévention primaire par le DAI, mais aussi des améliorations potentielles du pronostic rythmique grâce aux dernières avancées dans le traitement médicamenteux, le seuil de 35% pourrait éventuellement être remis en cause, ce d'autant que l'évaluation IRM de la FEVG, comme cela a été montré, donne des valeurs inférieures à l'échographie bidimensionnelle.

Il serait intéressant de refaire les analyses secondaires de notre travail en associant la présence de RT à la FEVG-IRM, afin d'évaluer si la présence de fibrose myocardique discrimine différemment la mortalité et les thérapies appropriées. D'autre part, il faudrait essayer de déterminer un seuil spécifique de FEVG-IRM pour l'indication d'implantation de façon prospective. Il est probable qu'il sera inférieur au seuil de 35% en échographie même si notre valeur de 22% est peut-être un peu basse pour l'envisager. Par ailleurs, il serait

intéressant de travailler sur les patients ayant une FEVG un peu moins altérée, et qui sont plus à risque d'être classés différemment selon l'examen d'imagerie utilisé. Joshi et al. avaient montré qu'une FEVG-2D entre 25 et 40% était associée au risque de reclassification par l'IRM. (18) C'est peut-être plus particulièrement pour ces patients que l'IRM revêt une importance particulière en permettant d'avoir accès à une donnée de FEVG plus reproductible et probablement plus robuste que celle mesurée par échographie bidimensionnelle, tout en donnant une information supplémentaire sur la fibrose comme marqueur de risque de MS. On pourrait à plus long terme envisager de réfléchir à l'indication prophylactique de façon différente : proposer l'implantation pour une FEVG inférieure à une valeur basse par exemple 25%, quelle que soit la méthode d'imagerie utilisée, et pour les patients ayant une FEVG entre 25 et 40% en échographie, compléter par une IRM, et par d'autres examens permettant d'évaluer le risque rythmique comme la scintigraphie de perfusion au $^{23}$mIBG déjà évoquée en introduction. Une autre problématique soulevée ces dernières années est celle des patients ayant une CMD. Dans notre étude, nous avions voulu analyser de façon séparée les patients, selon l'étiologie de l'IC-FEr. Nous avions retrouvé, au sein du sous-groupe de patients ischémiques, que la FEVG-IRM moyenne était significativement plus basse chez ceux ayant subi le critère primaire que chez les patients indemnes (22% versus 25%, p=0.027), et que la FEVG-2D tendait à l'être également (27% versus 29%, p=0.088). Au contraire, parmi les patients porteurs de CMD, il n'y avait aucune différence entre la FEVG (IRM ou 2D) selon la survenue ou non du critère primaire. Cependant, cette analyse de sous-groupe souffrait d'un échantillonnage trop faible, surtout en ce qui concernait le groupe CMD (n=53) par rapport au groupe ischémique (n=120), pour permettre de tirer des conclusions fiables de ces observations. Néanmoins, une autre série a déjà rapporté cette absence de différence de FEVG-IRM en cas de CMD, selon la survenue d'un critère associant thérapie appropriée, arrêt cardiaque récupéré ou MS, alors que la FEVG-IRM était significativement plus basse en cas d'évènement chez les patients ischémiques. (28) Ces données peuvent laisser penser que l'altération de la FEVG seule n'est pas un critère suffisant pour prédire la MS en cas de CMD, ce qui pourrait rendre compte des résultats de DANISH et renforcer l'intérêt d'y ajouter d'autres

marqueurs de risque de MS comme la fibrose. Par ailleurs, chez les patients pour lesquels l'indication de prévention primaire est moins discutable, l'information de RT fournie par l'IRM, comme marqueur de risque de MS, reste une donnée intéressante pouvant faire envisager un renforcement si possible du traitement médical ou envisager l'ablation par RF.

Après la stimulation conventionnelle et le DAI prophylactique, nous nous sommes penchés sur une autre problématique de sélection des patients pouvant bénéficier d'une thérapeutique rythmologique invasive : la RC par stimulation multisite chez le patient gériatrique. Est-il légitime de proposer un PM-RC, voire un DAI-RC, à un patient de 75 ans et plus ? Tout d'abord, la définition du patient âgé n'est pas universelle. L'OMS définit les individus de plus de 60 ans comme âgés, et, traditionnellement, étaient considérés âgés les patients de plus de 65 ans car il s'agissait de l'âge moyen de la retraite dans le monde. Cependant, l'allongement de la durée de vie, et de la durée de vie en bonne santé a rendu ces seuils quelque peu obsolètes. Dans les études plus récentes sur l'IC, les patients âgés avaient 70-80 ans, les patients de plus de 85 ans étant plutôt considérés comme « très âgés ». (29,30) Comme nous l'avons déjà exposé précédemment, les patients de plus de 70 ans étaient peu nombreux dans les essais sur la RC. Même si les données des analyses post-hoc des études MIRACLE et MIRACLE-ICD rapportaient une amélioration fonctionnelle et de la FEVG similaires au sein des différents groupes d'âge, les données objectives manquent chez ces patients. (31) Quelques séries ayant rapporté la faisabilité de la RC chez les patients âgés, l'application des recommandations générales de RC chez ces patients semble une option envisageable. (32–35)

Néanmoins, de nombreuses particularités des patients âgés peuvent compromettre ce postulat. Tout d'abord, les caractéristiques de l'IC sont différentes avec l'âge avancé. Le vieillissement s'accompagne de modifications de la structure et de la physiologie cardiaque, présentes même chez les patients n'ayant pas de cardiopathie sous-jacente. Il existe une perte et une altération fonctionnelle des cardiomyocytes, secondaires à des phénomènes

d'apoptose et accompagnées d'une hypertrophie compensatrice des cellules restantes, associées à des anomalies du métabolisme calcique, un raccourcissement des télomères et une fibrose extra-cellulaire. Ces anomalies vont favoriser chez les patients âgés l'apparition d'un phénotype d'IC-FEp. (36) Par ailleurs, la prévalence des comorbidités associées augmente (FA, HTA, maladies cérébro-vasculaires, troubles cognitifs, insuffisance rénale, anémie, cancers), et les symptômes classiques de l'IC sont parfois absents ou peu spécifiques, au profit de symptômes tels que l'asthénie, l'anorexie, la diminution de l'indice de masse corporelle. Cette notion de vulnérabilité plus importante chez les patients âgés est désormais identifiée sous le terme de syndrome de fragilité. De nombreux outils ont été développés pour l'évaluer, mais sans consensus clair, rendant les résultats des différentes études sur le sujet difficiles à comparer. En général, cinq aspects définissant le phénotype de fragilité sont évalués : lenteur, faiblesse, diminution d'activité physique, épuisement, fonte musculaire. La prévalence de ce syndrome est estimée entre 10 et 60% parmi les patients présentant des pathologies cardiovasculaires, variable selon le type de pathologie considérée, le score utilisé et le seuil retenu. Il a été montré dans des études épidémiologiques que les patients présentant ces critères de fragilité connaissent une morbi-mortalité doublée par rapport aux autres patients, qu'il s'agisse d'IC, de syndromes coronariens, d'interventions chirurgicales ou percutanées. (37) L'étude FRAIL-HF a été menée au sein d'une cohorte de 450 patients, de 70 ans et plus hospitalisés pour IC, afin d'évaluer l'impact de la fragilité sur le devenir des patients âgés. Une fragilité, définie par la positivité d'au moins trois des cinq critères précédents, était retrouvée chez 78% des patients, et associée à une dégradation fonctionnelle à 30 jours, une augmentation de la mortalité à un an, et des réhospitalisations pour IC à un an. (38) Une autre particularité des patients âgés atteints d'IC, est la fréquence des troubles cognitifs associés, qui sont en général d'autant plus sévères que l'IC est avancée, et qui sont associés à une dégradation pronostique avec un allongement des hospitalisations, une augmentation de la mortalité à un an. (39) Tous ces facteurs concourent à une vulnérabilité plus importante, et il est légitime de s'inquiéter sur ce terrain des éventuelles complications d'une intervention pour l'implantation d'une RC. Les données publiées sont

rassurantes et cohérentes avec nos résultats, ne rapportant pas d'augmentation des complications liées à la procédure chez les patients âgés. (32–34,40,41) Cependant, comme notre travail, ces données sont observationnelles, sur des séries limitées, et potentiellement sujettes à des biais de sélection, qui peuvent mener à une sous-estimation des complications chez les patients âgés.

En ce qui concerne l'effet sur la mortalité, les données sont également insuffisantes, mais plusieurs auteurs rapportent une mortalité un peu supérieure chez les patients âgés, (32,41,42) mais peu différente de celle de la population générale du même âge. (43,44) De plus, deux études menées chez des patients octogénaires appareillés d'un DAI-RC ont rapporté des taux de chocs appropriés significativement inférieurs à ceux des patients plus jeunes. (45,46) La situation de fin de vie chez la personne âgée doit aussi être prise en compte. En effet, la perception de la prévention de la MS évolue avec l'âge, d'autant plus s'il s'agit d'un patient en IC, pour lequel le bénéfice d'éviter une MS rythmique peut ne pas paraître évident. Certaines publications se sont intéressées à cette situation, et il apparaît qu'une proportion non négligeable de patients reçoit des chocs appropriés avant un décès par IC terminale, sources de douleur, d'anxiété, sans qu'une discussion sur la désactivation des thérapies ne soit souvent engagée. (47,48) Ces considérations doivent probablement inciter à évaluer au cas par cas l'intérêt d'associer un DAI à la RC chez les patients de plus de 80 ans, ou plus tôt selon l'état général et les comorbidités associées, et à envisager plutôt un PM-RC chez les plus fragiles, en tenant compte du souhait du patient.

D'autre part, l'optimisation du traitement médicamenteux de l'IC chez les patients âgés est difficile, et souvent plus longue à obtenir, pour plusieurs raisons. Le vieillissement s'accompagne en effet de modifications physiologiques qui augmentent le risque d'effets indésirables des médicaments, comme l'augmentation de la rigidité de l'arbre vasculaire artériel, l'altération de la réponse à l'orthostatisme, les modifications du débit hépatique, et de la fonction rénale. De plus, les patients âgés sont souvent sujets à la polymédication, et plusieurs sociétés de gériatrie ont proposé des outils afin de limiter les prescriptions non

nécessaires et éviter certaines interactions. D'un autre côté, les molécules recommandées dans la stratégie optimale de prise en charge de l'IC sont souvent sous prescrites, et, quand elles le sont, à des doses sub-optimales. (49) Enfin, les patients âgés posent également le problème d'une plus mauvaise adhérence au traitement/régime par rapport à des patients plus jeunes, ce phénomène étant tenu pour responsable d'environ un tiers des hospitalisations. (50) La place de la RC, dans la stratégie thérapeutique de l'IC chez les patients âgés, reste donc également à définir : après optimisation du traitement médicamenteux comme chez les patients plus jeunes ? Cette application stricte des recommandations peut conduire à trop retarder l'implantation, alors qu'il s'agit de patients ayant une espérance de vie plus modeste. Faut-il au contraire y penser rapidement chez un patient âgé, même non optimisé, au risque que cela soit prématuré ? Même si la RC peut être bénéfique chez certains patients âgés, il faut tenir compte de toutes ces particularités liées au vieillissement, raison pour laquelle il est important de réussir à sélectionner les « bons » candidats dans cette population fragile.

C'est pourquoi nous avons cherché à mettre en évidence des facteurs de réponse clinique à la RC chez les patients âgés de notre cohorte, pour savoir s'ils différaient de ceux des patients plus jeunes. Aucune donnée spécifique n'a été publiée, en revanche, plusieurs équipes ont proposé des scores de prédiction de la réponse à la RC, dans lesquels l'âge intervient, mais avec des résultats discordants. Maas et al. avaient mis en évidence que l'âge <60 ans était associé à un remodelage ventriculaire gauche favorable, alors que l'âge >75 ans était associé à l'absence d'amélioration. (51) Dans une autre publication, l'âge ≥70 ans était un facteur prédictif de mortalité après l'implantation d'une RC. (52) Au contraire, l'âge >70 ans était un des éléments du score élaboré afin de prédire la réponse échographique à la RC dans une cohorte française publiée en 2014. (53) Dans notre population, l'âge n'était pas un facteur corrélé au critère clinique de réponse (survie à un an sans hospitalisation pour IC et avec une amélioration d'au moins une classe NYHA), ni à la mortalité toute cause.

Dans l'étude RAFT, menée chez des patients en FA relevant d'une RC, le DAI-RC n'avait pas montré d'amélioration d'un critère associant mortalité et hospitalisations pour IC, par rapport

au DAI seul. (54) Nous n'avons retrouvé cet impact négatif de la FA sur la réponse à la RC que chez les patients de moins de 75 ans, à la fois en analyse uni et multivariée. Nous n'avons pas relevé le pourcentage de stimulation biventriculaire chez les patients en FA selon les groupes d'âge, ni les taux d'ablation de la jonction nodo-hissienne. Cependant, on peut envisager que, la diminution de la perméabilité de la voie de conduction auriculo-ventriculaire chez les patients plus âgés permette d'obtenir un taux de stimulation biventriculaire élevé dès l'implantation, et donc éviter, en partie, la perte d'efficacité liée à la FA observée chez les patients plus jeunes.

Le résultat probablement le plus important est que, parmi les patients âgés, le stade NYHA ≥3 au moment de l'implantation était un facteur prédictif fort de la survie à un an sans hospitalisations pour IC et associée à une amélioration du stade fonctionnel d'au moins une classe (HR=6,02; IC 95% 1,33 à 18,77, p=0,002), avec un effet neutre sur la mortalité. Au sein de la cohorte multicentrique française DAI-PP, les facteurs associés à la réponse à la RC ont été analysés, et contrairement à nos résultats, le stade NYHA ≤3 à l'implantation était un facteur prédictif indépendant de survie à un an sans hospitalisations pour IC, avec une amélioration du stade NYHA d'au moins une classe et/ou de la FEVG d'au moins 5%. L'âge moyen de cette cohorte était de 64,5 ans alors que l'âge moyen de notre groupe ≥75 ans était de 79 ans. (55) Les patients en stade IV ambulatoire de l'étude COMPANION avaient une amélioration du critère composite, mortalité et hospitalisations toutes causes, par le PM-RC et le DAI-RC, mais sans amélioration significative de la survie. (56) D'autres données sont en faveur d'un bénéfice moins marqué de la RC, et d'une mortalité plus élevée, chez les patients en stade IV de la NYHA, comparés à des patients moins sévères. (52,57) Ces données ont incité les cliniciens à ne pas envisager trop tardivement la RC chez un patient, pour éviter l'évolution vers l'IC avancée plus difficile à inverser. Le fait que nos patients âgés les plus symptomatiques tirent plus bénéfice de la RC peut sembler incohérent avec ces données. Une des explications possibles de ce résultat est peut-être une mauvaise évaluation du retentissement de l'IC chez le sujet âgé par le stade NYHA. En effet, comme nous l'avons

expliqué précédemment, la symptomatologie des patients âgées est différente. Il existe de nombreux facteurs confondants, non liés à l'IC, qui peuvent aggraver la dyspnée ou sa perception, comme les pathologies pulmonaires, l'asthénie ou la fatigabilité, qui sont multifactorielles et pas seulement secondaires à l'IC. Finalement, même si nos résultats ne permettent pas de résoudre la question de la RC chez le sujet âgé, ils confortent l'idée qu'il s'agit d'une thérapeutique envisageable malgré l'âge avancé, même chez des patients ayant une symptomatologie sévère au vu du stade NYHA, ou en FA. Il est probable que l'évaluation de la fragilité et de l'état cognitif des patients constituent des facteurs pronostiques plus importants que l'âge lui-même, qu'il serait intéressant de pouvoir tester de façon prospective.

Le dernier axe de ce projet était tourné vers l'autre grand volet de la prise en charge rythmologique des patients en IC, à savoir les traitements interventionnels des arythmies, et plus particulièrement l'ablation de FA. Nous avons développé dans l'introduction, les interactions négatives entre l'IC, quelle que soit sa forme clinique, et la survenue de FA, qui constituent le rationnel supportant une prise en charge basée sur le contrôle du rythme. Cependant, la stratégie de contrôle du rythme dans un contexte d'IC n'avait pas montré de supériorité sur le contrôle de la fréquence dans les études médicamenteuses. (58) La prise en charge non médicamenteuse pour le maintien du rythme sinusal chez les patients en FA s'est développée dans les années 1980, d'abord sur le plan chirurgical. L'hypothèse prédominante pour expliquer la FA étant la réentrée, le principe de l'ablation chirurgicale était de réaliser des lignes de bloc de conduction dans les oreillettes, aboutissant à leur segmentation électrique, afin d'empêcher la perpétuation des phénomènes de réentrée. Cela a donné naissance à la technique du « Maze », d'abord uniquement chirurgicale, les lignes étant réalisées par section-suture, puis au moyen d'outils non chirurgicaux comme la pince bipolaire. (59,60) Ces techniques permettaient le maintien en rythme sinusal dans 70 à 80% des cas, chez des patients programmés pour une chirurgie valvulaire ou coronarienne. Cependant, la nécessité d'une chirurgie à thorax ouvert avec circulation extra-corporelle rendait l'intervention trop

lourde pour l'envisager chez des patients sans indication chirurgicale autre, pour le seul traitement de la FA.

C'est donc l'ablation par voie endocavitaire percutanée qui s'est secondairement développée. Un certain nombre d'équipes ont tenté d'adapter la technique du Maze chirurgical à l'AC, mais avec des résultats modestes et des taux de complications élevés. Le rôle des veines pulmonaires, et plus particulièrement de leurs connexions ostiales à la musculature de l'oreillette, a été suspecté grâce à l'amélioration des connaissances sur l'anatomie fonctionnelle des oreillettes. La mise en évidence, par l'équipe Bordelaise, de foyers atriaux automatiques ectopiques au niveau des veines pulmonaires, capables de décharger une activité électrique rapide déclenchant des épisodes de FA, a été à l'origine de la stratégie consistant à isoler les veines pulmonaires. (61) L'IVP est devenue, et reste la pierre angulaire du traitement interventionnel de la FA. Cependant les récurrences restent fréquentes, surtout chez les patients présentant une FA persistante. Les mécanismes physiopathologiques responsables de la perpétuation de la FA font intervenir le remodelage atrial, et moins les veines pulmonaires, raison pour laquelle plusieurs techniques de modulation du substrat à l'aide de lésions complémentaires ont été proposées. Les stratégies proposées sont nombreuses, segmentation par des lignes, ablation des ganglions parasympathiques, des potentiels fragmentés, des foyers d'activité rotationnelle ; mais pour l'instant, aucune ne s'est imposée pour améliorer les résultats de l'ablation. L'étude STAR-AF II avait cherché à montrer l'intérêt de ces lésions supplémentaires, à l'époque l'ablation des potentiels fragmentés ou l'ablation linéaire, par rapport à l'IVP seule, sans parvenir à montrer de différence sur la récurrence de FA à 18 mois. (62)

Les techniques ont également évolué, RF point par point, cryothérapie au ballon, et plus récemment les autres techniques d'ablation au ballon comme le laser. Les cathéters d'ablation équipés de système de mesure du contact avec le tissu ont été proposés pour améliorer l'efficacité des lésions et les résultats des procédures, mais aussi réduire les complications. Des séries observationnelles ont montré des résultats encourageants, mais aucune étude

prospective de plus grande ampleur n'a permis de confirmer ces résultats, en ne permettant pas de réduire les récurrences à long terme ni les complications procédurales comme les tamponnades, qui sont, par ailleurs, devenues rares dans les centres experts. (63,64) De mêmes, les systèmes de CEA ont été proposé, pour guider les procédures d'ablation, réduire les durées de fluoroscopie et mieux comprendre les mécanismes des arythmies. Cependant, il n'y a pas de données concluantes sur l'amélioration des résultats à long terme grâce à la CEA. Néanmoins, et malgré le coût plus important des procédures guidées par CAE, ces systèmes ont été largement adoptés par les électrophysiologistes du monde entier. (65) Les patients en situation d'IC et présentant une arythmie atriale constituent un groupe hétérogène de situations avec des patients présentant de la FA paroxystique, d'autres des formes plus ou moins persistantes, une proportion non négligeable de patients ayant déjà eu une ou plusieurs procédures d'ablation, et se présentant avec une récidive, sous la forme de FA ou d'une TA organisée. Les mécanismes les plus fréquents sont alors des macro-réentrées, flutters typiques dépendant de l'isthme cavotricuspide ou atypiques, aux dépens d'un bloc incomplet sur une précédente ligne d'ablation, autour d'une zone de tissu cicatriciel, ou d'un obstacle anatomique. Il peut également s'agir de micro-réentrée (< 2cm) ou plus rarement d'une activité focale. La complexité de ces TA cicatricielles est souvent corrélée à l'importance du remodelage du substrat, dépendant des lésions d'ablation précédemment réalisées (IVP seule, ablation linéaire complémentaire, ou large ablation du substrat), de la dilatation des oreillettes, de la pathologie atriale sous-jacente, et à l'importance de la fibrose myocardique. Pour l'ablation de ces TA, la compréhension du circuit et l'identification de l'isthme critique/foyer sont essentiels pour espérer un succès pérenne de l'ablation. Les techniques d'entraînement permettent aux électrophysiologistes entraînés de comprendre la plupart des tachycardies, mais il existe toujours un risque d'arrêt de la TA par l'entraînement, ou d'erreurs d'interprétation, par exemple en cas de difficulté à stimuler une oreillette très pathologique, nécessitant une énergie importante pouvant capturer une trop large zone de tissu. Les systèmes de CEA permettent l'acquisition de cartes d'activation des tachycardies, avec moins de risque d'arrêt de la TA qu'avec l'entraînement, et qui permettent parfois de mieux

comprendre des TA complexes, notamment quand il existe plusieurs zones de bloc et/ou boucles. Cependant les systèmes de CEA conventionnels nécessitent une validation manuelle point par point, ce qui limite le nombre d'électrogrammes acquis pour l'élaboration d'une carte. C'est pourquoi le système UHD Rhythmia™ (Boston Scientific, Inc., Marlborough, MA, USA) présente, à priori, un intérêt majeur. Le cathéter permet l'acquisition simultanée des électrogrammes enregistrés par les 64 électrodes réparties sur les huit branches du cathéter dédié en forme de panier. Celles-ci sont de conception différente de ce qui existe dans les autres systèmes, puisqu'il s'agit de circuits imprimés de 0.4mm², espacés de 2.5mm, permettant de diminuer le bruit électrique, et d'améliorer la précision de l'acquisition. De plus, le système permet une acquisition automatisée en continu à partir de réglages prédéfinis, a une sensibilité accrue pour diminuer le seuil de détection des zones de cicatrice, et permet de créer en quelques minutes des cartes de plusieurs milliers de points, afin de comprendre les mécanismes de tachycardies complexes. Plusieurs séries observationnelles, publiées ces dernières années, ont montré la faisabilité et la sécurité d'utilisation du système, après une courbe d'apprentissage de quelques procédures, et son intérêt pour la compréhension de TA complexes, permettant parfois de corriger des erreurs d'annotation obtenues avec un autre système. (66–68) D'autres publications ont évalué son utilisation pour guider des procédures d'IVP, montrant encore une fois sa faisabilité, mais aussi une concordance modeste avec la détection par un cathéter lasso conventionnel. Dans 69% des cas, il s'agissait d'authentiques signaux veineux non vus par le lasso conventionnel, cependant dans 31% des cas, il s'agissait d'une surdétection d'un farfield atrial, pouvant résulter en une sous-estimation du résultat de l'IVP. (66,69,70) Cependant, ces différentes données sont basées sur des rapports d'expérience, sans tentative de comparaison avec une technique de référence, que ce soit l'électrophysiologie conventionnelle ou les systèmes de CEA classiques.

C'est dans ce contexte que nous avons voulu analyser et rapporter les résultats de nos ablations de TA, toutes guidées par une CEA, soit conventionnelle (Carto™ ou Ensite™), soit UHD par le Rhythmia™. De façon intéressante et bien que cela n'ait pas été un critère

d'inclusion dans cette étude, une majorité des patients avait une cardiopathie sous-jacente, et environ 50% d'entre eux étaient considérés comme IC (antécédent d'IC clinique et/ou FEVG<50%), sans différence entre les groupes. La FEVG moyenne de la population était de 49±15%, avec, cette fois, une différence entre les groupes, car les patients du groupe Rhythmia™ avait une FEVG à 52±13% comparée à 46±16% dans le groupe contrôle (p=0,04). Nous avons donc mis en évidence un nombre plus important de cartes réalisées, et plus d'électrogrammes enregistrés avec le système UHD, avec une durée de procédure ayant tendance à être plus longue, mais pas de différence de durée de fluoroscopie. De plus, nous avons rapporté une réduction des récidives de TA à un an dans le groupe Rhythmia™, sans différence en termes de complications, mais avec une proportion plus importante de patients IC dans le groupe contrôle. Ces patients étant plus fragiles, il est d'autant plus important de réussir à améliorer les taux de maintien en rythme sinusal au décours de l'AC, tout en évitant les complications liées à la procédure.

C'est pour cette raison que nous avons poursuivi ces travaux en nous intéressant plus particulièrement aux résultats des AC guidées par le système Rhythmia™ chez des patients IC, que la FEVG soit préservée ou pas, comparés à des patients non-IC. Assez peu de comparaisons directes ont été réalisées concernant les résultats de l'ablation de FA entre des patients IC et non-IC. En ce qui concerne la sécurité des procédures, Tondo et al. avaient rapporté un taux plus important de complications chez des patients ayant une altération de la FEVG et traités au moyen d'un système de CEA. (71) Ces résultats sont déjà assez anciens, et de nombreuses publications ont permis de conclure à la faisabilité de ces procédures chez les patients IC. (65) Cependant, les procédures Rhyhtmia™ sont un peu plus longues, comme nous l'avons montré ainsi que Kosiuk et al, (72) le cathéter diagnostique est également irrigué en plus du cathéter d'ablation, contrairement aux autres cathéters diagnostiques utilisés avec les systèmes conventionnels. C'est pour ces raisons qu'il était légitime de se poser la question de la sécurité de ces procédures chez des patients IC, classiquement plus à risque de complications en cas de procédures prolongées, et plus sensible au remplissage. Cependant,

nos résultats sont rassurants, puisqu'en dépit de comorbidités plus importantes, les patients du groupe IC n'ont pas rencontré plus de complications, avec des taux comparables à ceux de la littérature, en particulier pas de complications hémodynamiques, même chez ceux ayant une altération de la FEVG. Le seul indicateur que nous avons retrouvé était le recours plus fréquent à une augmentation des diurétiques chez les patients IC, ce qui n'est pas une surprise, car c'est un phénomène que nous observons souvent chez les IC, après les ablations RF quel que soit le système de CEA utilisé. Le registre TRUE-HD, récemment publié et qui constitue la plus grande série publiée sur l'utilisation de ce système UHD, a confirmé l'absence de surrisque lié à ces procédures ou au cathéter dédié. (73) D'autres séries ont montré la faisabilité de ces procédures dans des catégories de patients à risque, comme les enfants ou les patients porteurs de cardiopathie congénitale. (74,75)

Concernant les résultats de l'ablation, nous n'avons pas mis en évidence de différence sur les récidives d'arythmie entre les patients IC et non-IC, ni entre les patients avec ou sans altération de la FEVG. Si le rôle délétère de la FA chez les patients IC-FEp a été montré il y a déjà presque 10 ans, il n'y a eu que très peu de publications sur l'intérêt de l'ablation chez ces patients. Cha et al. avaient rapporté des résultats intermédiaires, sur un critère de maintien en rythme sinusal à un an sans antiarythmique, en cas d'altération de la fonction diastolique, moins bons qu'en cas de fonction cardiaque normale, mais meilleurs qu'en cas d'altération de la FEVG. (76) Plus récemment, Black-Maier et al. ont comparé les résultats de l'ablation de FA paroxystique et persistante, chez des patients IC-FEr/m et IC FEp en utilisant le même critère de FEVG que le nôtre. Il s'agissait de procédures guidées par une CEA classique (Carto™ ou Ensite™). Ils ont constaté, comme nous, un taux de maintien en rythme sinusal similaire dans les deux groupes, et une amélioration fonctionnelle associée à un remodelage favorable échographique après l'ablation, avec des taux de complications majeures identiques et cohérents avec la littérature actuelle. (77) Finalement, nos taux de récurrence sont un peu plus faibles que ceux publiés dans l'ablation de FA et l'IC, ce qui est possiblement dû au nombre important de TA inclues, plus de la moitié des procédures de chaque groupe. En effet,

nous savons que les résultats à long-terme de l'ablation en cas de FA persistante sont moins satisfaisants que pour les autres arythmies, ce qui s'est confirmé dans cette étude, la FA persistante étant un facteur associé à la récurrence. De même, les autres facteurs associés à la récurrence, étaient la fuite mitrale, qui aggrave la surcharge et le remodelage atrial, et la cardiomyopathie hypertrophique, ce qui peut s'expliquer par l'hypertrophie atriale, rendant plus difficile l'obtention de lésions de RF efficaces et pérennes, comme cela a été déjà proposé. (78,79)

Il faudrait très probablement confirmer ces résultats de façon prospective, en comparant les résultats obtenus avec la cartographie UHD et les autres systèmes, et en étudiant de plus grandes cohortes de patients présentant une IC-FEp et IC-FEm pour mieux définir l'intérêt et la place de l'AC de la FA et des TA chez eux. En ce qui concerne les autres systèmes de cartographie, les versions les plus récentes (Carto3™, Ensite Precision™) évoluent également vers l'UHD, tant au niveau des cathéters diagnostiques que des softwares. Si ces outils semblent améliorer la compréhension des mécanismes des tachycardies (isthme critique d'une TA, activité rotationnelle en FA par exemple) et nous donnent, électrophysiologistes, l'impression de procédures plus efficaces, il faut que ces résultats se traduisent par l'amélioration du maintien en rythme sinusal, notamment pour les patients présentant des TA récidivantes après plusieurs procédures, ou de la FA persistante, mais aussi du pronostic de l'IC. Si CASTLE-AF a confirmé les attentes en améliorant un critère comprenant la mortalité et les hospitalisations pour IC chez des patients IC-FEr, CABANA n'a pas réussi à confirmer cela dans une population moins sélectionnée. C'est pourquoi, d'autres travaux seront nécessaires pour valider la place de l'ablation de la FA dans la stratégie globale de prise en charge de l'IC. En effet, ces outils augmentent de façon significative le prix des procédures. Compte-tenu de l'augmentation de la prévalence de ces pathologies (FA, IC) et des indications d'ablation, la question du coût pourrait devenir un enjeu pour les centres. Des études médico-économiques seront donc également les bienvenues pour mettre en balance les dépenses

liées aux procédures avec les économies réalisées par exemple par les diminutions d'hospitalisations pour IC.

## PERSPECTIVES

Les études que nous avons menées devront être suivies d'autres projets. En ce qui concerne l'intérêt potentiel des algorithmes de détection automatique du SAS dans les prothèses, PM et DAI, il faudrait réussir à établir des profils de patients à risque de développer une IC ou de l'aggraver. On pourrait à cet effet, suivre de façon prospective prolongée les patients dont la prothèse est équipée du SAM (ou un programme équivalent), et associer les données du suivi (RDI, arythmies, etc.) à la survenue d'un évènement clinique, IC aigue, AVC, décès. Il serait également intéressant d'évaluer l'impact du SAM sur le dépistage du SAS en pratique clinique, en comparant deux groupes de patients, SAM activé dans le groupe actif et désactivé dans le groupe contrôle. En parallèle, chez les patients traités par PPC, nous pourrions comparer l'évolution du RDI à l'IAH donné par le ventilateur, et aux données de compliance comme la durée de port du masque.

Dans le domaine de l'éligibilité au DAI pour la prévention primaire de la MS, nous avons le projet d'une comparaison prospective de patients par IRM et échographie 3D, notamment ceux ayant une FEVG-2D entre 25 et 35%, afin d'affiner les seuils de FEVG permettant de prédire les évènements rythmiques, en y associant le RT, ou des paramètres cliniques.

En ce qui concerne l'évaluation de place de la RC dans la prise en charge de l'IC chez le sujet âgé, nous souhaitons évaluer l'impact du niveau cognitif sur la survenue de complications et sur la réponse clinique à la RC chez des patients de plus de 80 ans.

Enfin, dans le domaine de l'ablation de FA, plus particulièrement la FA persistante, nous voudrions évaluer de façon prospective différentes stratégies d'ablation, ablation linéaire, des potentiels fragmentés, ou encore des zones d'activité rotatoire, à la fois en cas d'IC-FEr et d'IC-FEp/m, guidées par la cartographie UHD.

## CONCLUSION

Ces différents travaux ont permis d'apporter des éléments de réponse à différentes questions qui se posent, concernant le versant rythmologique de la prise en charge des patients IC. Tout d'abord, nous avons souligné l'intérêt des nouveaux algorithmes proposés par les PM, qui permettent chez des patients à haut risque d'IC, de dépister efficacement le SAS et d'en assurer la surveillance après traitement, simplifiant ainsi le suivi de ces patients souvent âgés. L'utilisation de ces outils s'inscrit dans une démarche de prise en charge adaptée aux phénotypes particuliers présentés par les patients en situation d'IC, plus particulièrement en l'absence d'altération sévère de la FEVG. Puis nous avons souligné l'intérêt de la multimodalité en imagerie pour mieux identifier les patients à risque de MS et poser l'indication d'un DAI prophylactique, en combinant l'évaluation de la FEVG par échographie avec l'IRM, permettant, outre la mesure de la FEVG, d'obtenir des informations sur le substrat arythmogène. Par ailleurs, nous avons mis en évidence que les patients gériatriques, même avec un stade NYHA avancé ou en FA, pouvaient bénéficier de la RC aussi bien que les patients plus jeunes, sans plus de complications à craindre. Enfin nous avons également discuté l'intérêt d'une nouvelle cartographie UHD pour guider les ablations d'arythmies supraventriculaires complexes en cas d'IC. Ce système est utilisable sans augmentation de la morbidité interventionnelle, avec une efficacité similaire sur le maintien en rythme sinusal des patients IC comparés à des patients contrôles, et permet une amélioration fonctionnelle significative des patients IC. Des travaux supplémentaires permettront de continuer à préciser l'intérêt de ces résultats pour aider à résoudre les incertitudes persistant aujourd'hui dans la prise en charge rythmologique de l'IC.

**Bibliographie de la discussion**


1. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart J. 2014 Oct 21;35(40):2797–815.

2. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321–60.

3. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003 Jan 8;289(2):194–202.

4. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA. 2011 Aug 24;306(8):856–63.

5. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep Apnea and Cardiovascular Disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Journal of the American College of Cardiology. 2008 Aug 19;52(8):686–717.

6. Escourrou P, Meslier N, Raffestin B, Clavel R, Gomes J, Hazouard E, et al. [Which clinical approach and which diagnostic procedures for obstructive sleep apnea syndrome?]. Rev Mal Respir. 2010 Oct;27 Suppl 3:S115-123.

7. El Shayeb M, Topfer L-A, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. CMAJ. 2014 Jan 7;186(1):E25-51.

8. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007 Dec 15;3(7):737–47.

9. Place et conditions de réalisation de la polysomnographie et de la polygraphie respiratoire dans les troubles du sommeil - Rapport d'évaluation [Internet]. Haute Autorité de Santé. [cited 2019 Sep 22]. Available from: https://www.has-sante.fr/jcms/c_1056842/fr/place-et-conditions-de-realisation-de-la-polysomnographie-et-de-la-polygraphie-respiratoire-dans-les-troubles-du-sommeil-rapport-d-evaluation

10. Garrigue S, Pépin J-L, Defaye P, Murgatroyd F, Poezevara Y, Clémenty J, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. Circulation. 2007 Apr 3;115(13):1703–9.

11. Defaye P, Pépin J-L, Poezevara Y, Mabo P, Murgatroyd F, Lévy P, et al. Automatic recognition of abnormal respiratory events during sleep by a pacemaker transthoracic impedance sensor. J Cardiovasc Electrophysiol. 2004 Sep;15(9):1034–40.

12. Defaye P, de la Cruz I, Martí-Almor J, Villuendas R, Bru P, Sénéchal J, et al. A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. Heart Rhythm. 2014 May;11(5):842–8.

13. Moubarak G, Bouzeman A, de Geyer d'Orth T, Bouleti C, Beuzelin C, Cazeau S. Variability in obstructive sleep apnea: Analysis of pacemaker-detected respiratory disturbances. Heart Rhythm. 2017 Mar;14(3):359–64.

14. D'Onofrio A, La Rovere MT, Emdin M, Capucci A, Sinagra G, Bianchi V, et al. Implantable cardioverter-defibrillator-computed respiratory disturbance index accurately identifies severe sleep apnea: The DASAP-HF study. Heart Rhythm. 2018;15(2):211–7.

15. Defaye P, Mendelson M, Tamisier R, Jacon P, Venier S, Arnol N, et al. Validation of an apnea and hypopnea detection algorithm implemented in implantable cardioverter defibrillators. The AIRLESS study. Sci Rep. 2019 Jul 3;9(1):9597.

16. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787–847.

17. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000 Aug;21(16):1387–96.

18. Joshi SB, Connelly KA, Jimenez-Juan L, Hansen M, Kirpalani A, Dorian P, et al. Potential clinical impact of cardiovascular magnetic resonance assessment of ejection fraction on eligibility for cardioverter defibrillator implantation. J Cardiovasc Magn Reson. 2012;14:69.

19. Rijnierse MT, van der Lingen A-LCJ, Weiland MTD, de Haan S, Nijveldt R, Beek AM, et al. Clinical Impact of Cardiac Magnetic Resonance Imaging Versus Echocardiography-Guided Patient Selection for Primary Prevention Implantable Cardioverter Defibrillator Therapy. Am J Cardiol. 2015 Aug 1;116(3):406–12.

20. Rayatzadeh H, Patel SJ, Hauser TH, Ngo LL, Shaw JL, Tan A, et al. Volumetric Left Ventricular Ejection Fraction is Superior to 2-Dimensional Echocardiography for Risk Stratification of Patients for Primary Prevention Implantable Cardioverter-Defibrillator Implantation. The American Journal of Cardiology. 2013 Apr 15;111(8):1175–9.

21. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996 Dec 26;335(26):1933–40.

22. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002 Mar 21;346(12):877–83.

23. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005 Jan 20;352(3):225–37.

24. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NAM, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004 May 20;350(21):2151–8.

25. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H, et al. EHRA White Paper: knowledge gaps in arrhythmia management-status 2019. Europace. 2019 Mar 18;

26. Desai AS, McMurray JJV, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015 Aug 7;36(30):1990–7.

27. de Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018;15(3):395–402.

28. Gao Peng, Yee Raymond, Gula Lorne, Krahn Andrew D., Skanes Allan, Leong-Sit Peter, et al. Prediction of Arrhythmic Events in Ischemic and Dilated Cardiomyopathy Patients Referred for Implantable Cardiac Defibrillator. Circulation: Cardiovascular Imaging. 2012 Jul 1;5(4):448–56.

29. Barsheshet A, Shotan A, Cohen E, Garty M, Goldenberg I, Sandach A, et al. Predictors of long-term (4-year) mortality in elderly and young patients with acute heart failure. Eur J Heart Fail. 2010 Aug;12(8):833–40.

30. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. Eur Heart J. 2009 Feb;30(4):478–86.

31. Kron J, Aranda JM, Miles WM, Burkart TA, Woo GW, Saxonhouse SJ, et al. Benefit of cardiac resynchronization in elderly patients: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. J Interv Card Electrophysiol. 2009 Aug;25(2):91–6.

32. Achilli A, Turreni F, Gasparini M, Lunati M, Sassara M, Santini M, et al. Efficacy of cardiac resynchronization therapy in very old patients: the Insync/Insync ICD Italian Registry. Europace. 2007 Sep;9(9):732–8.

33. Delnoy PPHM, Ottervanger JP, Luttikhuis HO, Elvan A, Misier ARR, Beukema WP, et al. Clinical response of cardiac resynchronization therapy in the elderly. Am Heart J. 2008 Apr;155(4):746–51.

34. Foley PWX, Chalil S, Khadjooi K, Smith REA, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronization therapy in octogenarians: a comparative study with a younger population. Europace. 2008 Nov;10(11):1302–7.

35. Brambatti M, Guerra F, Matassini MV, Cipolletta L, Barbarossa A, Urbinati A, et al. Cardiac resynchronization therapy improves ejection fraction and cardiac remodelling regardless of patients' age. Europace. 2013 May;15(5):704–10.

36. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail. 2013 Jul;15(7):717–23.

37. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014 Mar 4;63(8):747–62.

38. Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail. 2016;18(7):869–75.

39. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, et al. Cognitive Impairment and Heart Failure: Systematic Review and Meta-Analysis. J Card Fail. 2017 Jun;23(6):464–75.

40. Höke U, Putter H, Van Der Velde ET, Schalij MJ, Delgado V, Bax JJ, et al. Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. Circ Cardiovasc Qual Outcomes. 2014 May;7(3):437–44.

41. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J, et al. Response to cardiac resynchronization therapy in elderly patients (≥70 years) and octogenarians. Eur J Heart Fail. 2013 Feb;15(2):203–10.

42. Killu AM, Wu J-H, Friedman PA, Shen W-K, Webster TL, Brooke KL, et al. Outcomes of cardiac resynchronization therapy in the elderly. Pacing Clin Electrophysiol. 2013 Jun;36(6):664–72.

43. Rickard J, Cheng A, Spragg D, Green A, Leff B, Tang W, et al. Survival in octogenarians undergoing cardiac resynchronization therapy compared to the general population. Pacing Clin Electrophysiol. 2014 Jun;37(6):740–4.

44. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Mode of Death in Octogenarians Treated With Cardiac Resynchronization Therapy. J Card Fail. 2016 Dec;22(12):970–7.

45. Kelli HM, Merchant FM, Mengistu A, Casey M, Hoskins M, El-Chami MF. Intermediate-term mortality and incidence of ICD therapy in octogenarians after cardiac resynchronization therapy. J Geriatr Cardiol. 2014 Sep;11(3):180–4.

46. Adelstein EC, Liu J, Jain S, Schwartzman D, Althouse AD, Wang NC, et al. Clinical outcomes in cardiac resynchronization therapy-defibrillator recipients 80 years of age and older. Europace. 2016 Mar;18(3):420–7.

47. Goldstein NE, Lampert R, Bradley E, Lynn J, Krumholz HM. Management of implantable cardioverter defibrillators in end-of-life care. Ann Intern Med. 2004 Dec 7;141(11):835–8.

48. Lampert R, Hayes DL, Annas GJ, Farley MA, Goldstein NE, Hamilton RM, et al. HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy. Heart Rhythm. 2010 Jul;7(7):1008–26.

49. Bader F, Atallah B, Brennan LF, Rimawi RH, Khalil ME. Heart failure in the elderly: ten peculiar management considerations. Heart Fail Rev. 2017 Mar 1;22(2):219–28.

50. Giardini A, Martin MT, Cahir C, Lehane E, Menditto E, Strano M, et al. Toward appropriate criteria in medication adherence assessment in older persons: Position Paper. Aging Clin Exp Res. 2016 Jun;28(3):371–81.

51. Maass AH, Vernooy K, Wijers SC, van 't Sant J, Cramer MJ, Meine M, et al. Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study. Europace. 2018 01;20(2):e1–10.

52. Khatib M, Tolosana JM, Trucco E, Borràs R, Castel A, Berruezo A, et al. EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors. Eur J Heart Fail. 2014 Jul;16(7):802–9.

53. Brunet-Bernard A, Maréchaux S, Fauchier L, Guiot A, Fournet M, Reynaud A, et al. Combined score using clinical, electrocardiographic, and echocardiographic parameters to predict left ventricular remodeling in patients having had cardiac resynchronization therapy six months earlier. Am J Cardiol. 2014 Jun 15;113(12):2045–51.

54. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2012 Sep 1;5(5):566–70.

55. Providencia R, Marijon E, Barra S, Reitan C, Breitenstein A, Defaye P, et al. Usefulness of a clinical risk score to predict the response to cardiac resynchronization therapy. Int J Cardiol. 2018 01;260:82–7.

56. Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation. 2007 Jan 16;115(2):204–12.

57. Castel MÁ, Magnani S, Mont L, Roig E, Tamborero D, Méndez-Zurita F, et al. Survival in New York Heart Association class IV heart failure patients treated with cardiac resynchronization therapy compared with patients on optimal pharmacological treatment. Europace. 2010 Aug 1;12(8):1136–40.

58. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008 Jun 19;358(25):2667–77.

59. Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 1/2-year clinical experience with surgery for atrial fibrillation. Ann Surg. 1996 Sep;224(3):267–73; discussion 273-275.

60. Gaynor SL, Diodato MD, Prasad SM, Ishii Y, Schuessler RB, Bailey MS, et al. A prospective, single-center clinical trial of a modified Cox maze procedure with bipolar radiofrequency ablation. J Thorac Cardiovasc Surg. 2004 Oct;128(4):535–42.

61. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998 Sep 3;339(10):659–66.

62. Verma A, Jiang C, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015 May 7;372(19):1812–22.

63. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque J-P, Kautzner J, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath

Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. Circulation. 2015 Sep 8;132(10):907–15.

64. Ullah W, McLean A, Tayebjee MH, Gupta D, Ginks MR, Haywood GA, et al. Randomized trial comparing pulmonary vein isolation using the SmartTouch catheter with or without real-time contact force data. Heart Rhythm. 2016;13(9):1761–7.

65. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. Europace. 2018 Jan 1;20(1):157–208.

66. Sohns C, Saguner AM, Lemes C, Santoro F, Mathew S, Heeger C, et al. First clinical experience using a novel high-resolution electroanatomical mapping system for left atrial ablation procedures. Clin Res Cardiol. 2016 Dec;105(12):992–1002.

67. Schaeffer B, Hoffmann BA, Meyer C, Akbulak RÖ, Moser J, Jularic M, et al. Characterization, Mapping, and Ablation of Complex Atrial Tachycardia: Initial Experience With a Novel Method of Ultra High-Density 3D Mapping. J Cardiovasc Electrophysiol. 2016 Oct;27(10):1139–50.

68. Anter E, McElderry TH, Contreras-Valdes FM, Li J, Tung P, Leshem E, et al. Evaluation of a novel high-resolution mapping technology for ablation of recurrent scar-related atrial tachycardias. Heart Rhythm. 2016;13(10):2048–55.

69. Anter E, Tschabrunn CM, Contreras-Valdes FM, Li J, Josephson ME. Pulmonary vein isolation using the Rhythmia mapping system: Verification of intracardiac signals using the Orion mini-basket catheter. Heart Rhythm. 2015 Sep 1;12(9):1927–34.

70. Santoro F, Sohns C, Saguner AM, Brunetti ND, Lemes C, Mathew S, et al. Endocardial voltage mapping of pulmonary veins with an ultra-high-resolution system to evaluate atrial myocardial extensions. Clin Res Cardiol. 2017 Apr 1;106(4):293–9.

71. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, et al. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing Clin Electrophysiol. 2006 Sep;29(9):962–70.

72. Kosiuk J, Hilbert S, John S, Bertagnolli L, Hindricks G, Bollmann A. Preliminary experience with high-density electroanatomical mapping for ablation of atrial fibrillation - Comparison of mini-basket and novel open irrigated magnetic ablation catheter in consecutive patients. Int J Cardiol. 2017 Feb 1;228:401–5.

73. Hindricks G, Weiner S, McElderry T, Jaïs P, Maddox W, Garcia-Bolao JI, et al. Acute safety, effectiveness, and real-world clinical usage of ultra-high density mapping for ablation of cardiac arrhythmias: results of the TRUE HD study. Europace. 2019 Apr 1;21(4):655–61.

74. Mori H, Muraji S, Sumitomo N, Kato R, Imamura T, Komori A, et al. Safety and accuracy of the Rhythmia mapping system in pediatric patients. Heart Rhythm. 2019 Mar;16(3):388–94.

75. Ernst S, Cazzoli I, Guarguagli S. An initial experience of high-density mapping-guided ablation in a cohort of patients with adult congenital heart disease. Europace. 2019 Jan 1;21(Supplement_1):i43–53.

76. Cha Y-M, Wokhlu A, Asirvatham SJ, Shen W-K, Friedman PA, Munger TM, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):724–32.

77. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. Heart Rhythm. 2018;15(5):651–7.

78. Suenari K, Nakano Y, Hirai Y, Ogi H, Oda N, Makita Y, et al. Left atrial thickness under the catheter ablation lines in patients with paroxysmal atrial fibrillation: insights from 64-slice multidetector computed tomography. Heart Vessels. 2013 May;28(3):360–8.

79. Zhao D-S, Shen Y, Zhang Q, Lin G, Lu Y-H, Chen B-T, et al. Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. Europace. 2016 Apr;18(4):508–20.

## Nouvelles perspectives diagnostiques et thérapeutiques dans la prise en charge rythmologique des patients en situation d'insuffisance cardiaque

Laure CHAMP-RIGOT

**RESUME**

L'insuffisance cardiaque est un problème de santé publique dans les pays développés, touchant 1 à 2% de la population générale, mais dont la prévalence atteint 10% après 70 ans. Les progrès thérapeutiques ont permis d'améliorer le pronostic des patients, notamment ceux ayant une altération de la fonction systolique ventriculaire gauche. Les troubles du rythme sont fréquents et nécessitent une pris en charge particulière au cours des situations d'insuffisance cardiaque. Cependant, il reste des questions non résolues : comment améliorer l'efficacité du traitement de l'insuffisance cardiaque à fonction systolique préservée, comment mieux sélectionner les patients pouvant bénéficier de la prévention primaire de la mort subite par un défibrillateur implantable, les patients âgés peuvent-ils bénéficier de la même prise en charge que les patients plus jeunes, et pour finir comment améliorer les résultats de l'ablation de fibrillation auriculaire dans les situations d'insuffisance cardiaque. Nous avons mis en place une étude prospective chez des patients présentant une dysfonction diastolique pour évaluer l'intérêt de l'algorithme de surveillance de l'apnée du sommeil disponible dans des stimulateurs cardiaques. En parallèle, nous avons analysé l'impact de l'évaluation par résonance magnétique des patients candidats à un défibrillateur sur la prédiction des évènements rythmiques, mais aussi le devenir des patients de plus de 75 ans appareillés avec un système de resynchronisation cardiaque. Enfin, nous nous sommes intéressés aux résultats d'un nouveau système de cartographie électroanatomique ultra-haute densité pour guider les procédures d'ablation de troubles du rythme supraventriculaires complexes chez des patients insuffisants cardiaques comparés à des patients contrôles.

**MOTS-CLES** : insuffisance cardiaque ; syndrome d'apnée du sommeil, mort subite, resynchronisation cardiaque, fibrillation auriculaire, ablation par cathéter

# Heart failure management from the electrophysiologist's point of view: Perspectives in diagnostic and therapeutic approach

Laure CHAMP-RIGOT

**ABSTRACT**

Heart failure is a major public health issue in developed countries, with a prevalence of 1-2% of global population, rising to 10% after 70 years of age. Therapeutic progresses have succeeded in improving patients' prognosis, particularly in case of reduced left ventricular ejection fraction. Rhythm abnormalities are frequent, and need special consideration in case of heart failure. Meanwhile, there are still some gaps in the evidence: heart failure with preserved systolic function is complex and difficult to treat, primary prevention of sudden cardiac death is effective but there is a need to better select candidates, whether elderly patients should be treated as younger individuals, and finally how to improve outcomes of atrial fibrillation catheter ablation. Firstly, we have conducted a prospective study to evaluate the Sleep Apnea Monitoring algorithm provided in a novel pacemaker in patients with diastolic dysfunction. Besides, we analyzed whether magnetic resonance imaging could predict cardiac outcomes in patients with an implantable cardioverter defibrillator better than echocardiography. We also reported the outcomes of the cardiac resynchronization therapy in patients ≥75 years old compared to younger patients. Finally, we studied the results of a novel ultra-high density mapping system to guide ablation procedures of complex atrial arrhythmias in heart failure patients compared to controls.

**KEY WORDS:** heart failure, sleep apnea syndrome, sudden cardiac death, cardiac resynchronization therapy, atrial fibrillation, catheter ablation