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Atrial Perfusion - Metabolism and Fibrosis in Atrial Fibrillolon

The TRIATLON project

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« Les chemins difficiles mènent souvent à de belles destinations »

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THESIS OUTLINE

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and affects millions of people worldwide, with significant repercussion on their life expectancy and quality of life. Its persistent form remains a challenge for the clinician because its pathophysiology and its association with atrial cardiomyopathy and left atrial (LA) remodeling are still incompletely understood. Recent imaging studies contributed to significant advances improving LA remodeling evaluation and management of AF. However, all imaging modalities available in clinical practices present limitations and pitfalls.

In this context, we started the multidisciplinary TRIATLON (Atrial Perfusion - Metabolism and Fibrosis in Atrial Fibrillation) project whose the main objective is to evaluate LA structural remodeling in patients with persistent AF, first through LA function evaluation with speckle tracking echography, then with LA glucose metabolism evaluation with ^{18}F -Fluorodeoxyglucose Positron Emission Tomography (^{18}F -FDG PET).

Chapter 1 introduces the notion of AF. Epidemiology, clinical symptoms, related outcomes, guidelines for treatment and the imaging modalities to evaluate LA structural remodeling. Then we expose AF physiopathology and one aspect of the Coumel triangle: LA substrate, atrial remodeling and atrial cardiomyopathy with special focus on hemodynamics and energy demands in AF and the associated cellular metabolic changes.

The aims of the thesis are summarized in **chapter 2**.

Method and results are structured in **chapter 3** from 4 manuscripts:

- Article 1 evaluate the ability of Speckle Tracking Echography parameters acquired during persistent AF to assess atrial fibrosis measured by low voltage area, and to predict maintenance of sinus rhythm (SR) after catheter ablation.
- Article 2 describe the optimal reconstruction algorithm for metabolic evaluation of the LA using ^{18}F -FDG-PET/computed tomography.
- Article 3 highlights the fact that altered LA glucose metabolism by ^{18}F -FDG-PET in persistent AF normalizes after return to SR.
- Article 4 explore how to identify LA fibrosis and predict catheter ablation outcomes by ^{18}F -FDG PET/CT in persistent AF with a multimodal comparison.

Finally, **chapter 4** summarizes the main finding of this project and lays out future directions.

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LIST OF ABBREVIATIONS AND ACRONYMS:

- AAD: AntiArrhythmic Drugs
- AF : Atrial Fibrillation
- AFI : Atrial Flutter
- AFB : Atrial Fibrillation Burden
- AMPK: AMP-activated protein Kinase
- ANS: Autonomic Nervous System
- ATP: Adenosine TriPhosphate
- CFAE: Complex Fractionated Atrial Electrogram
- DAD: Delayed AfterDepolarizations
- EAVM : ElectroAnatomical Voltage Mapping
- EAT: Epicardial Adipose Tissue
- EEC : External Electrical Choc
- ERP: Effective Refractory Period
- ETC : Electron Transport Chain
- FA: Fatty Acids
- GLUT: Glucose Transporter
- GPALS : Global Peak Atrial Longitudinal Strain
- HFpEF: Heart Failure with preserved Ejection Fraction
- HFrEF: Heart Failure with reduced Ejection Fraction
- IAS : InterAtrium Septum
- LAA : Left Atrial Appendage
- LA : Left Atrium
- LAVI: Left Atrial Volume Indexed
- LGE-cMR : Late Gadolinium Enhancement cardiac Magnetic Resonance
- LGU: Low Glucose Uptake
- LVA : Low Voltage Area
- LV : Left Ventricle
- NADH: Nicotinamide Adenine Dinucleotide Hydrogen
- NYHA: New York Heart Association functional status

- O₂: Oxygen
- PDH: Pyruvate DeHydrogenase
- PET : Positron Emission Tomography
- PV: Pulmonary Veins
- PVI: Pulmonary Veins Isolation
- PVE : Partial Volume Effect
- QoL: Quality of Life
- RA : Right Atrium
- RF: RadioFrequency
- ROI : Regio Of Interest
- ROS : Reactive Oxygen Species
- RV : Right Ventricle
- SAF : Silent Atrial Fibrillation
- SR: Sinus Rhythm
- STE: Speckle Tracking Echography
- SUV : Standardized Uptake Value
- SVT : Supra Ventricular Tachycardia
- TBR : Target to Background Ratio
- TTE : Trans-Thoracic Echocardiography
- TOE : Trans-Oesophageal Echocardiography
- VT : Ventricular Tachycardia
- ¹⁸F-FDG : ¹⁸FluoroDesoxyGlucose
- ⁶⁸Ga-FAPI : Gallium-68 Fibroblast Activation Protein Inhibitor
- mBq: micro Becquerel

- CHAPTER I – INTRODUCTION -

1. CHAPTER I – INTRODUCTION

1.1. Atrial Fibrillation (a clinical challenge)

1.1.1. History and definition

Since its age-old description by many physicians of the ancient China, Egypt and Greece (1) and its first electrocardiographic tracing published in 1906 by Willem Einthoven (1860-1927) (2), the understanding of the pathophysiological mechanisms of atrial fibrillation (AF) has considerably evolved. In its recent guidelines, the European Society of Cardiology defines AF as a supraventricular tachyarrhythmia (SVT) with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. Its electrocardiographic description is characterized by an irregularly irregular rhythm, absence of P waves, absence of isoelectric baseline, and variable ventricular response (see figure 1) (47).

It is the most common sustained cardiac arrhythmia and contributes greatly to cardiovascular morbidity and mortality. Despite the awareness of the stakes that it represents, many aspects of AF management remain controversial and constitute a challenge for the clinician.

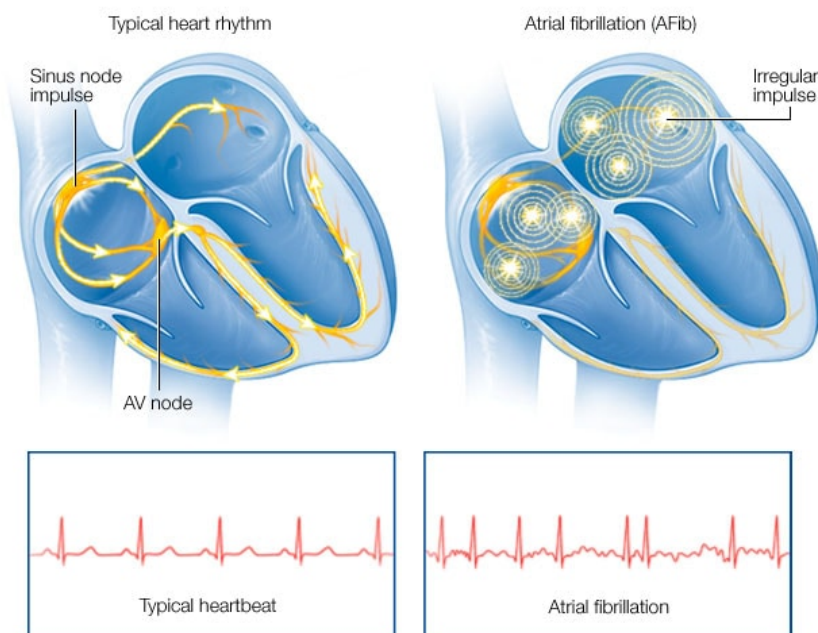


Figure 1: In a typical heart, a tiny group of cells at the sinus node sends out an electrical signal. The signal travels through the heart's upper chambers to the atrioventricular (AV) node. The signal then passes into the lower heart chambers, causing them to squeeze and pump out blood. In atrial fibrillation, electrical signals fire from many locations in the upper chambers, causing them to beat chaotically. Since the AV node doesn't prevent all of these chaotic signals from entering the lower chambers, the heart beats faster and irregularly. From Mayo foundation for medical education and research.

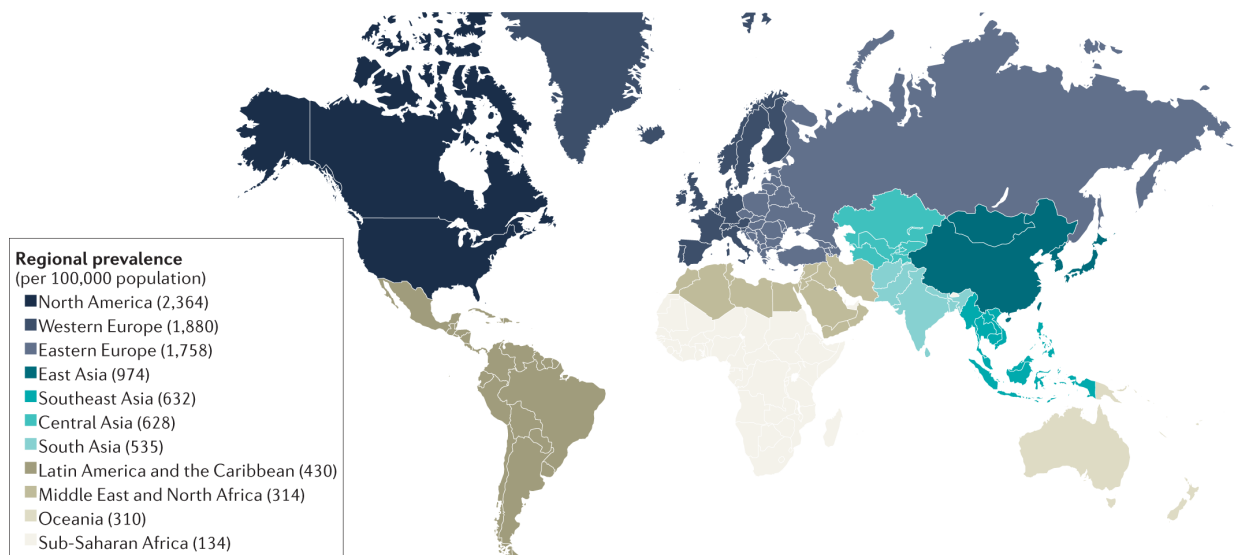


Figure 2: Regional prevalence (cases per 100,000 individuals) of AF. The map shows the regions of high prevalence (Western Europe and North America) and the generally lower prevalence in South Asia, Oceania and the Middle East. Data are from the Global Burden of Disease (GBD) Collaborative Network's GBD 2019 results. From Brundel BJM et al., Nat Rev Dis Primers. 2022 Apr 7;8(1):21.

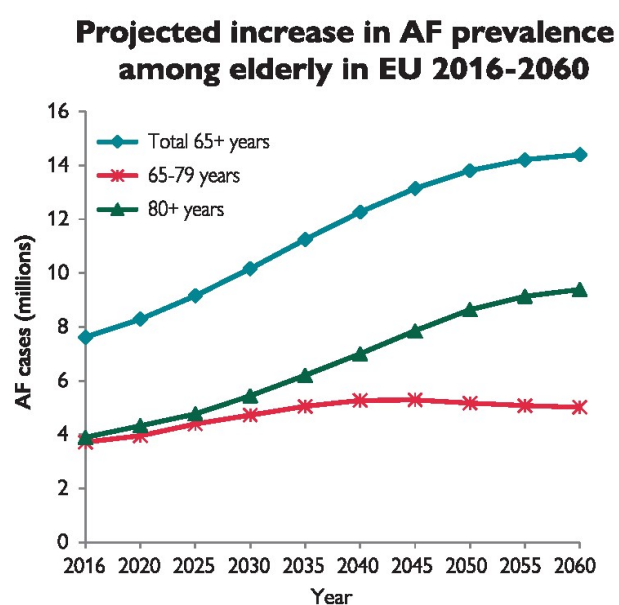


Figure 3: Epidemiology of AF: prevalence and projected rise in the incidence and prevalence from ESC guidelines Eur Heart J. 2021 Feb 1;42(5):373-498.

1.1.2. Epidemiology (AF a worldwide epidemic)

AF is a major burden to healthcare systems. Multiple studies of predominantly European and American populations indicate that the currently estimated prevalence of AF in adults is between 2% and 4% - about 4.5 million people in Europe (3)- and a 2.3-fold (4) rise is expected (5,6), owing to extended longevity in the general population and intensifying search for undiagnosed AF (see figure 2 and 3) (7). Increasing age is a prominent risk factor for AF, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease (8), obesity, and obstructive sleep apnoea represent also important (9- 13) modifiable risk factors and are potent contributors to AF development and progression (14,15).

Incidence rates increased from <0.5 to 2, to 3 to 9, and 10 to 39 cases per 1000 person-years at 50, 65, and 80 years, respectively (16-21). The lifetime risk of developing AF for individuals 40 to 55 years of age has been estimated to be 22% to 26% (22).

1.1.3. Clinical presentation of AF and AF-related outcomes

1.1.3.1. Clinical presentation of AF

Patients with AF may have various symptoms. The most common symptom is palpitation with sensation of a quivering or fluttering heartbeat. Additional common symptoms may be reported as general fatigue, dizziness, shortness of breath and anxiety, weakness, faintness or confusion, exercise intolerance, sweating or chest pain (23).

In about one-third of patients (50-87 % in some series) with this arrhythmia, patients are asymptomatic or not aware of the presence of AF (24,25). Therefore, the term silent atrial fibrillation (SAF), which refers to the occurrence and detection of subclinical asymptomatic episodes of paroxysmal AFib, emerged. To quantitate such episodes of SAF, the concept of atrial fibrillation burden (AFB) was introduced. AFB can be defined as the % of time spent in AF per unit of time (eg, day, week, month) and is also applicable for symptomatic AF, especially after ablation procedure to quantitate success rates (26,27).

Accordingly, the presentation of AF can range from asymptomatic to devastating complications such as cardiogenic shock and ischemic stroke (figure 4).

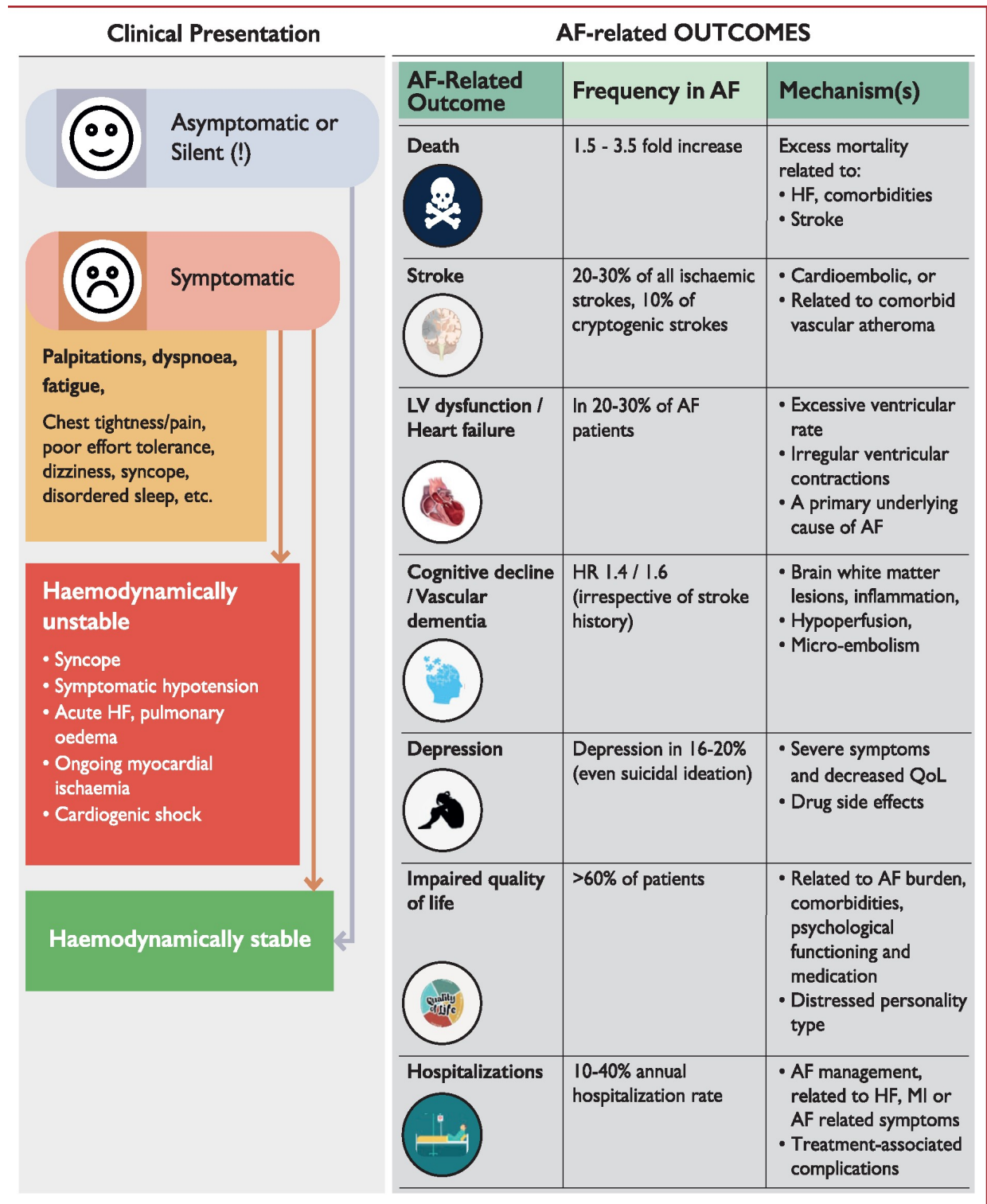


Figure 4: Clinical presentation of AF and AF-related outcomes. From ESC guidelines Eur Heart J. 2021 Feb 1;42(5):373-498.

1.1.3.2. AF-related outcomes

Stroke/systolic embolism are the most dreaded complication of AF. This arrhythmia is associated with a 5-fold increased risk of stroke and 20 to 30% of stroke events are due to AF (see figure 4). (47) The annual AF-related stroke risk depends on comorbidities and can be stratified using a point-based system: The CHA₂DS₂-VASc score (28, 29). Cardioembolic strokes associated with AF are usually severe, highly recurrent, often fatal, or with permanent disability (30). In a population-based registry, patients with new-onset AF also had increased rates of systemic embolism (31). For a few years, the pathophysiology of stroke associated with AF is currently being questioned. The linear sequence traditionally described in arrhythmia, blood stasis, intracavitary thrombus, and embolization to the central nervous system is incomplete. The concept of atrial cardiomyopathy and atrial remodeling where cardioembolism occurs in a non-AF dependent manner fits better with current data (32). This point will be developed later.

The left atrium (LA) is the barometer of the left ventricle (LV). Accordingly, **heart failure** with preserved (HFpEF) or reduced (HFrEF) ejection fraction is often associated with AF. The prevalence of AF in patients with HF increases as the disease worsens. In patients with functional classification NYHA I-II, the prevalence is typically around 5%. The prevalence increases to 26 % in NYHA III symptoms and up to 50% in NYHA IV. (33) Multiple AF-associated mechanisms/myocardial alterations may lead to LV dysfunction and HF: Hemodynamic effects with loss of atrial kick, reduction of cardiac output – by as much as 25% with diastolic dysfunction, loss of atrio-ventricular synchrony. Tachycardia effects with worsened ventricular function can lead to tachycardia-mediated cardiomyopathy, reduced filling time in tachycardia, reduced ejection time in tachycardia and greater prevalence of right ventricular dysfunction (34- 36). Finally, sharing common risk factors, AF and HF often coexist, or may precipitate/exacerbate each other, resulting in significantly greater mortality than either condition alone (37).

AF also significantly affects **Quality of life** (QoL) and patient functional status. More than 60% of AF patients have significantly impaired QoL or exercise tolerance. QoL is significantly lower in women, young individuals, and those with comorbidities (38, 39).

Patients with AF more often developed **anxiety disorders**, had a higher burden of depressive symptoms, and poorer QoL with a Distressed personality type (Type D) (40).

Cognitive impairment/dementia: AF may lead to cognitive impairment ranging from mild dysfunction to dementia via clinically apparent or silent stroke or insufficiently understood stroke-independent pathways (41-43).

Hospitalization: approximately 30% of AF patients have at least one, and 10% have > 2, hospital admissions annually. (44) The most common reasons for hospitalization of these patients were cardiovascular disorders (49%), non-cardiovascular causes (43%) and bleeding (8%) (45).

Mortality: AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men, with an overall 3.5-fold mortality risk increase. The mechanistic explanation for this association is multifaceted and associated comorbidities play an important role (46, 47).

1.1.3.3. AF subtypes

Different AF classifications have been proposed. The ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery distinguished five patterns of AF, based on presentation, duration and spontaneous termination of AF episodes (47):

AF pattern	Definition
First diagnosed	AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset.
Persistent	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after > 7 days
Long-standing persistent	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
Permanent	AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. Permanent AFib represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

Other classifications of AF reflect the presence of symptoms or underlying cause of AF are proposed by the AHA/ACC/HRS Guideline for the Management of Patients with AF.

Recommendations for AF management are not based on the temporal AF patterns, but preferably on a holistic approach to optimal management of these patients. Accordingly, structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of these patients at different healthcare levels, inform treatment decision-making, and facilitate optimal management of AF patients (recommendation class IIA, level of evidence C) (48).

1.1.3.4. AF, a progressive disease ?

For decades, the prevailing notion was that AF began with paroxysmal episodes that increased in frequency and duration causing progression to more persistent AF subtypes. This so-called “AF begets AF” postulate was based on early experimental data in goats, showing that tachycardia induces electrophysiological atrial remodeling resulting in persistence of AF. (49) Currently, AF is considered to be a progressive disease and the transition from paroxysmal to persistent or permanent AF is often characterized by advancing atrial structural remodeling or worsening of atrial cardiomyopathy. (50, 47) However, not all patients go through every phase, and the time spent in each can vary widely. Research over the past decades has identified a multitude of pathophysiological processes contributing to the initiation, maintenance, and progression of AF. (51)

Reported annual rates of paroxysmal AF progression range from <1% to 15% (up to 27 - 36% in studies with ≥ 10 -year follow-up). (52, 53) Risk factors for AF progression include age, HF, hypertension, chronic kidney diseases, chronic pulmonary diseases, diabetes mellitus, previous stroke, and LA size. (54) Progression to persistent/permanent AF is associated with adverse cardiovascular events, hospitalizations, and death (55).

1.1.4. Treatment: The “ABC” holistic pathway

The 2020 ESC Guidelines for the diagnosis and management of AF advocate a simple Atrial fibrillation Better Care (ABC) holistic pathway (‘A’ Anticoagulation/Avoid stroke; ‘B’ Better symptom management; ‘C’ Cardiovascular and Comorbidity optimization). (47)

1.1.4.1. ‘A’ - Anticoagulation/Avoid stroke

The use of oral anticoagulation in patients with AF at moderate or high risk of stroke, estimated by established criteria (56) and the CHA2DS2-VASc score (28,29), improves outcomes. However, to ensure that the benefits exceed the risks of bleeding, appropriate patient selection is essential. Vitamin K antagonists were the only oral anticoagulation treatment available until 2010. However, since more than one-decade, Non-vitamin K antagonist oral anticoagulants have become the mainstay of treatment. These oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) obviate many of warfarin’s shortcomings, and they have demonstrated safety and efficacy in large randomized trials of patients with non-valvular AF. (57-60) However, the management of patients taking oral anticoagulation remains a clinical challenge. There are several important considerations when selecting anticoagulant therapy for patients with AF; stroke risk assessment, bleeding risk assessment, absolute contraindications to oral anticoagulants, stroke prevention therapies, available agents (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, other), non-pharmacological alternative with left atrial appendage (LAA) occlusion and exclusion, and management of anticoagulation-related bleeding risk (47).

1.1.4.2. ‘B’ - Better symptom control

Although the management of AF historically focused on decreasing AF recurrence, it evolved over time in favor of rate control. (61-66) Recently, more emphasis has been placed rhythm control demonstrating that this treatment can reduce adverse cardiovascular outcomes (63,67,68), generally by using safe and effective rhythm-control therapies - typically antiarrhythmic drugs (AAD) and/or AF ablation. Evidence increasingly supports early rhythm control in patients with AF that has not become long-standing, (69) but current clinical practice and guidelines do not yet fully reflect this change. Early rhythm control may effectively reduce the self-perpetuating effect of AF through structural remodeling of the atria (70-72) and

prevent AF-related deaths, HF, and strokes in high-risk patients (69). It has the potential to halt progression and potentially save patients from years of symptomatic AF; therefore, it should be offered more widely (73). Since the late 20th century, there has been rapid development in catheter ablation for AF, evolving from an experimental procedure to an important treatment option for AF that is recommended in numerous guidelines. (47,74) Although ablation can be accompanied by acute/direct complications because of its complex interventional nature, which can result in collateral damage to nearby organs and structures, the complication rate has declined in recent years in experienced centers due to quality improvement initiatives and advancement in techniques and technologies (see figure 5). (75,76) Additionally, ablation is more effective than AADs for maintaining sinus rhythm, including when used as first-line treatment for rhythm control (77-80).

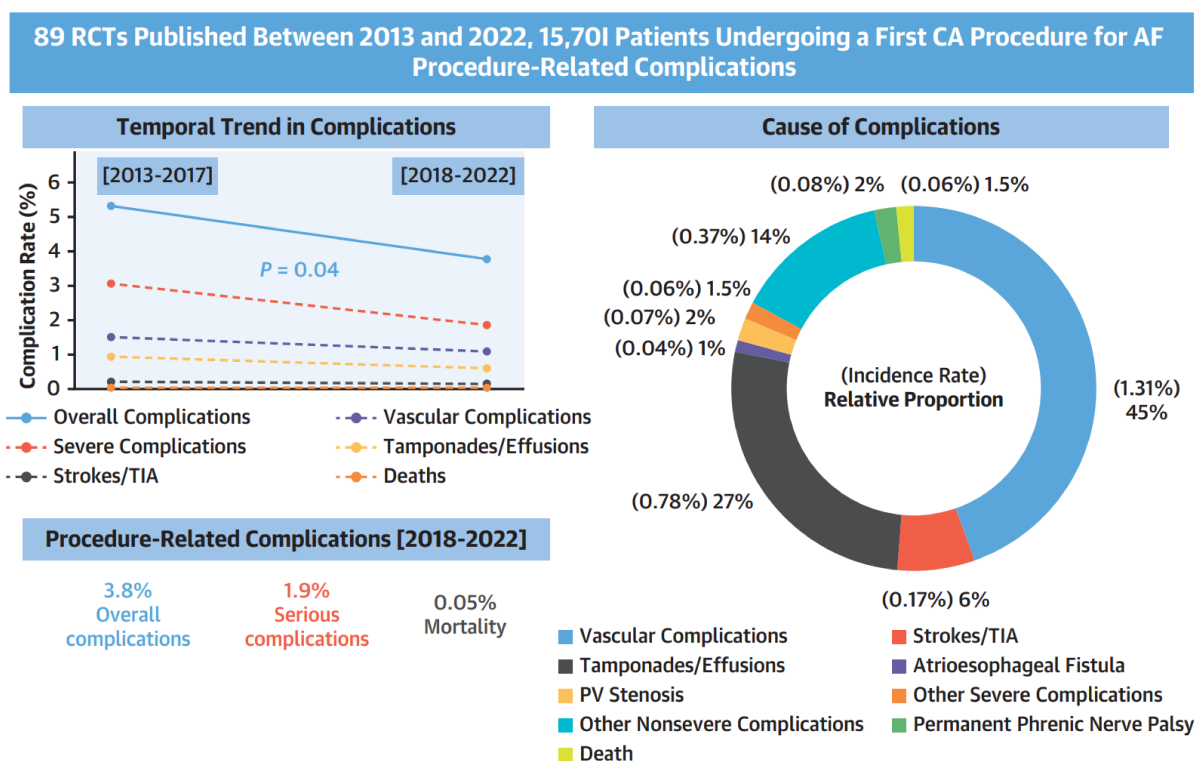
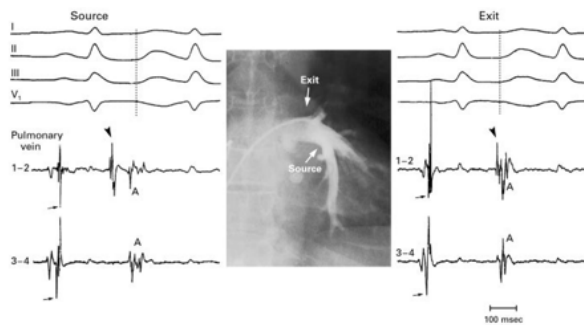


Figure 5: Temporal Trend in Procedure-Related Complications of Catheter Ablation for Atrial Fibrillation. This meta-analysis of 15,701 patients with a first catheter ablation (CA) procedure for atrial fibrillation (AF) found a significant reduction in the incidence of procedure-related complications (w30%) when the contemporary period of publication (2018-2022) was compared with the preceding period (2013-2017). The study provides current exclusively prospectively evaluated estimates of specific complication and mortality rates associated with CA procedures for AF. Relative proportions of the main complications are shown on the right. Isch 1/4 ischemic; PV 1/4 pulmonary vein; RCT 1/4 randomized control trial; TIA 1/4 transient ischemic attack. From Benali K, Khairy P, Hammache N, Petzl A, Da Costa A, Verma A, Andrade JG, Macle L. Procedure-Related Complications of Catheter Ablation for Atrial Fibrillation. *J Am Coll Cardiol.* 2023 May 30;81(21):2089-2099.



Angiogram of a Left Inferior Pulmonary Vein Depicting the Source and Exit of Ectopic Activity.

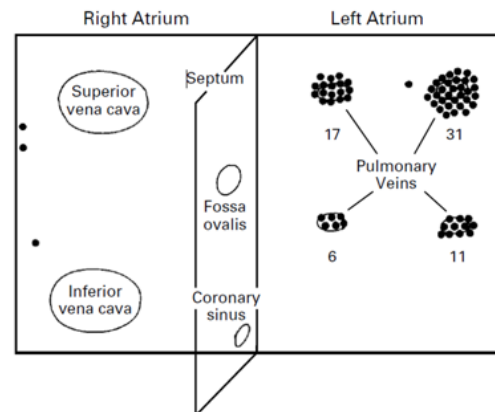


Diagram of the Sites of 69 Foci Triggering Atrial Fibrillation in 45 Patients

Figure 6: Spontaneous initiation of AF by ectopic beats originating in the PVs. From Haïssaguerre M. et al. *N Engl J Med.* 1998 Sep 3;339(10):659-66.

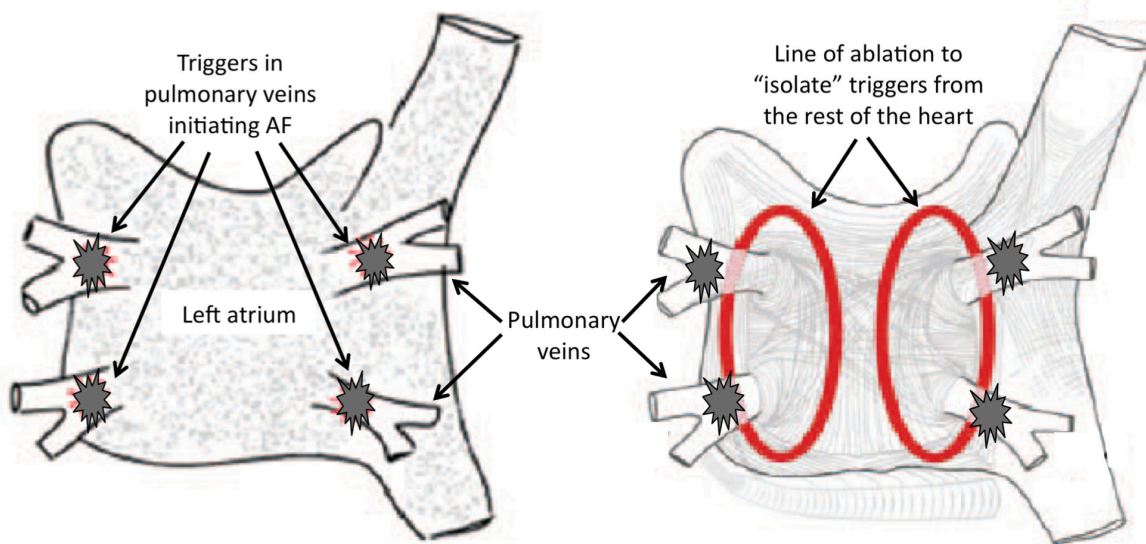


Figure 7: Schematic of common lesion sets employed in AF ablation with circumferential ablation lesions that are created in a circumferential fashion around the right and the left PVs. From 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017 Oct;14(10):e275-e444.

1.1.4.2.1. Pulmonary veins isolation, the cornerstone of AF Ablation.

Haïssaguerre et al. reported in 1998 that the ectopic electrical activity arising in pulmonary veins (PVs) was responsible for the initiation of AF (see figure 6). Since then, eliminating triggers with electrical isolation of the PV by creation of circumferential lesions around the right and the left PV ostia was emphasized as a reasonable approach to treat AF and became the cornerstone of AF catheter ablation procedure. (81, 82) A schematic overview of common lesion sets created during an AF ablation procedure is shown in figure 7. Several catheter designs with multiple energy sources have been developed. Among the 4 energy sources proposed (radiofrequency, cryoablation, pulsed field ablation and endoscopic laser), radiofrequency (RF) is the most evidence-based (see figure 8) (75). The effects of these lesions have been attributed to isolation of AF triggering PV foci, elimination of non-PV triggering foci, and/or as the result of modification of the arrhythmogenic substrate. (83) The latter might include interruption of crucial pathways of conduction between pulmonary-atrial junctions, which play a role in sustenance of AF, reduction of the amount of mass available for the number of simultaneously circulating wavelets (atrial debulking), or partial vagal denervation by interruption of vagal stimulation from the autonomic ganglia (75, 84-86).

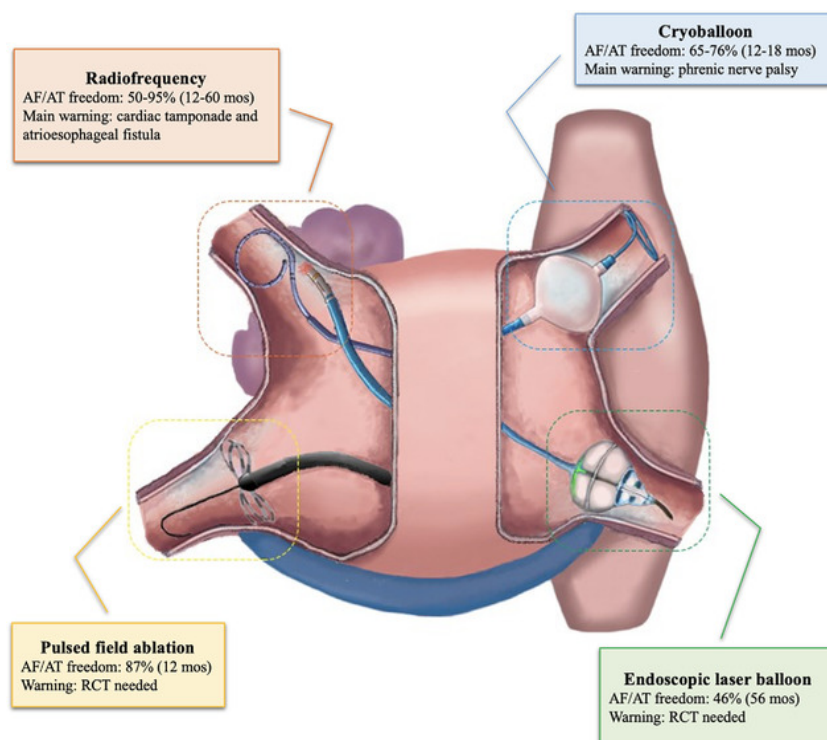
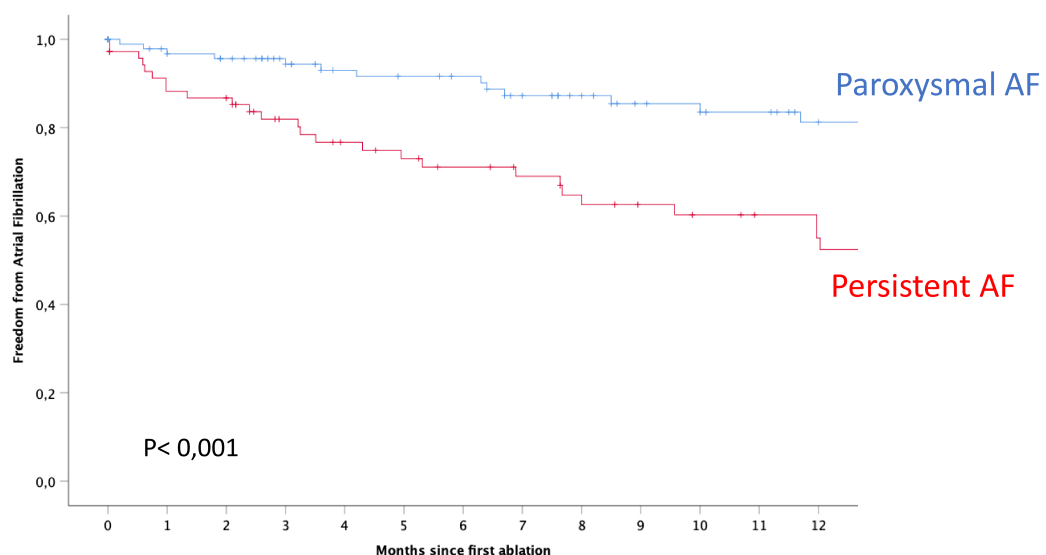


Figure 8: schematic representation of current energy sources and ablation outcomes after pulmonary vein isolation. From La Rosa G. et al. *Pacing Clin Electrophysiol.* 2021 Feb;44(2):341-359.

1.1.4.2.2. Success of AF Ablation

The multiple-procedure success rate of pulmonary vein isolation (PVI) in patients with paroxysmal AF after a 5-year follow-up period has been reported to be approximately 80%, falling to about 60% after 10 years (87,88). For patients with persistent AF, stable sinus rhythm (SR) after successful PVI was reported in 52% after a single procedure and in 65% after multiple procedures, during a median follow-up of approximately 7 years (89).

Our experience in Cliniques universitaires St-Luc confirms these findings: Between March 2019 and December 2021, we retrospectively studied 178 patients with non-valvular AF (106 paroxysmal AF and 72 persistent AF) undergoing PVI in our electrophysiology lab. Subjects had undergone complete follow-up with a clinical evaluation and 24 hours Holter monitoring within one year of ablation. The primary end point was freedom from any documented recurrence of atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) lasting longer than 30 seconds at follow-up. After 12 months, AF recurrence free survival rates were respectively 85% in patients with paroxysmal AF and 61 % with persistent AF patient (log-rank, $p < 0.001$) (see Figure 9).



AF	N total	event	Censored N	%
Parox	106	16	90	84,9%
Persist	72	28	44	61,1%
Global	178	44	134	75,3%

Figure 9 : Kaplan–Meier estimates of freedom from documented atrial fibrillation more than 30 seconds after a single AF ablation procedure, with or without the use of antiarrhythmic medications. From Marchandise et al. UCLouvain, Cliniques universitaires Saint-Luc experience 2019-2021. Unpublished data.

However, estimation of the real success rate after catheter ablation procedure remains difficult due to inconsistencies in the definitions of procedural success and post-procedural recurrences, differences in post-procedural rhythm monitoring strategies, and differences in the analysis of outcomes after single or multiple procedures. Moreover, these results shows that PVI has limited efficacy in treating persistent AF patients and support the fact that the persistent AF prognosis is often influenced by non-pulmonary vein triggers and/or another factor of the Coumel triangle (90): the LA substrate and LA structural remodeling with atrial fibrosis. Finally, some studies showed that current guidelines for classification of AF may not reflect clinical outcomes suggesting that the current definition of AF duration should be reevaluated (183, 184). Accordingly, the electrophysiology community realized that complete elimination of AF was untenable and that reduction in the frequency, duration, and overall symptoms associated with AF (AF burden) were an acceptable goal studies and may represent a more relevant parameter for risk stratification and efficacy assessment after ablation procedure (91).

1.1.4.2.3. The Ablative Strategy for persistent Atrial Fibrillation

The most recent European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation (75) stated that PVI is now widely accepted as the cornerstone of AF ablation procedures (47) and that electrical isolation of the PVs is recommended during all AF ablation procedures (Class I, LOE A). However, due to the high recurrence rate observed in patients with persistent and long-standing persistent AF with PVI alone, efforts continued to identify additive strategies to improve the outcomes of AF ablation. These strategies have included linear RF lesions in the LA and RA, ablation of autonomic ganglia, ablation by complex fractionated atrial electrogram (CFAE), ablation of non-PV foci, isolation of the LAA, ablation of scar identified by voltage mapping or cardiac Magnetic Resonance (cMR), ablation of rotational activity, and ablation of ligament of Marshall with vein of Marshall ethanol infusion (182) (see figure 10).

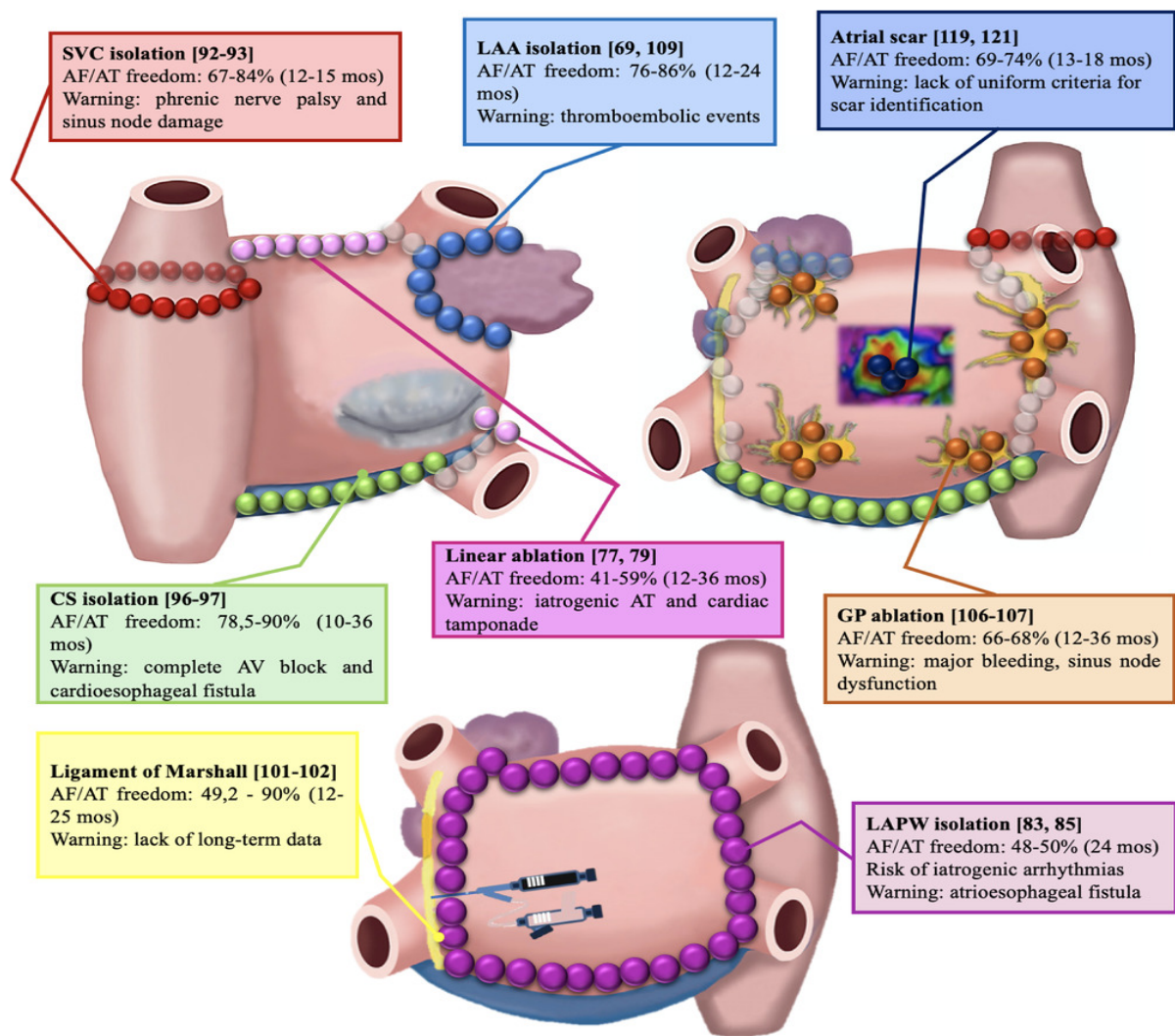


Figure 10: Current non-pulmonary vein strategies for atrial fibrillation ablation. AF: atrial fibrillation, AT: atrial tachycardia, AV : atrioventricular, CS :coronary sinus, LAA : left atrial appendage, LAPW: left atrial posterior wall, PVI: pulmonary vein isolation, SVC: superior vena cava. From La Rosa G. et al. *Pacing Clin Electrophysiol.* 2021 Feb;44(2):341-359.

For persistent and long-standing persistent AF, more extensive ablation has been advocated. However, additional benefit vs. PVI alone, justifying its use during the first procedure, is yet to be confirmed. (47, 75). For example STAR-AF2 have shown that a systematic CFAE ablation or additional linear lesion in persistent AF patient did not clearly demonstrate benefit when compared to PVI only. (92) Accordingly, to complete PVI in the persistent AF ablation population, the ablation strategy is increasingly moving towards a tailored approach based on:

- a non-PV “triggers” identification such as AV nodal reentry or accessory pathway-mediated AV reciprocating tachycardia, the posterior wall of the LA, the SVC, the crista terminalis, the fossa ovalis, the CS, the eustachian ridge, the ligament of Marshall, and adjacent to the AV valve annuli, autonomic ganglia, CFAE, ablation of rotational activity ablation of ligament of Marshall with vein of Marshall ethanol infusion (see figure 11) (75).
- The assessment of the substrate and the atrial remodeling with ablation of fibrosis identified by different imaging technology supported by studies, like ERASE AF, showing that individually tailored substrate modification guided by voltage mapping was associated with a significantly higher arrhythmia-free survival rate compared with a conventional approach applying linear ablation according to AF type (93-96) (see figure 12).

Whether any or all of these strategies will emerge as standard proven components to AF ablation procedures will be determined over time. Moreover, the results have been mixed. In order to better interpret them, a thorough understanding of atrial structural remodeling physiopathology and the place of several imaging modalities must be clarified (94-96).

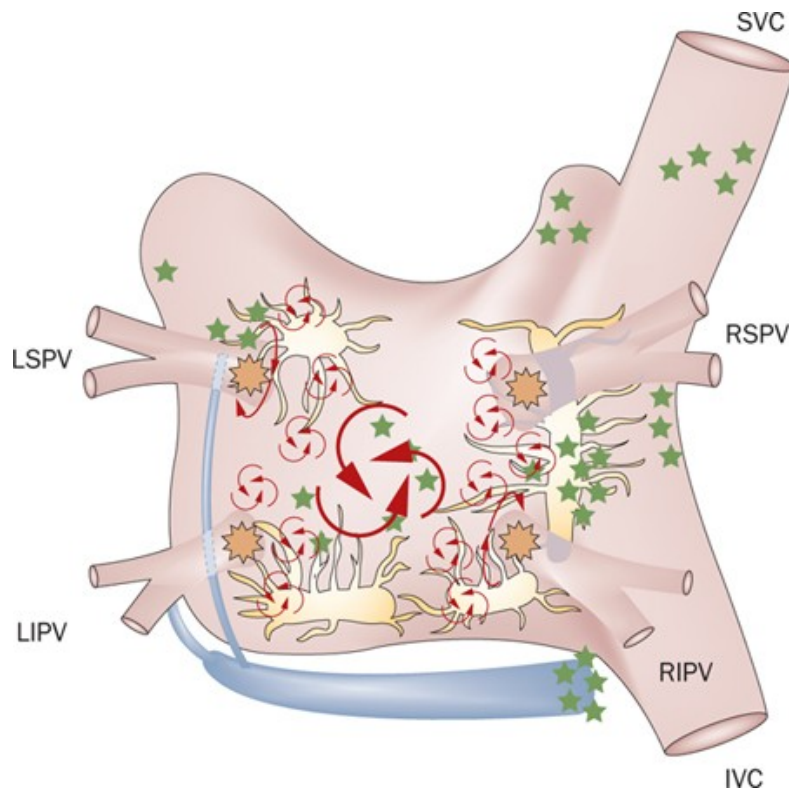


Figure 11: The anatomical and arrhythmic target of AF ablation procedure. From Nat Rev Cardiol. 2010 Mar;7(3):129-38.

The ERASE-AF trial

Low-Voltage Myocardium-Guided Ablation Trial of Persistent Atrial Fibrillation

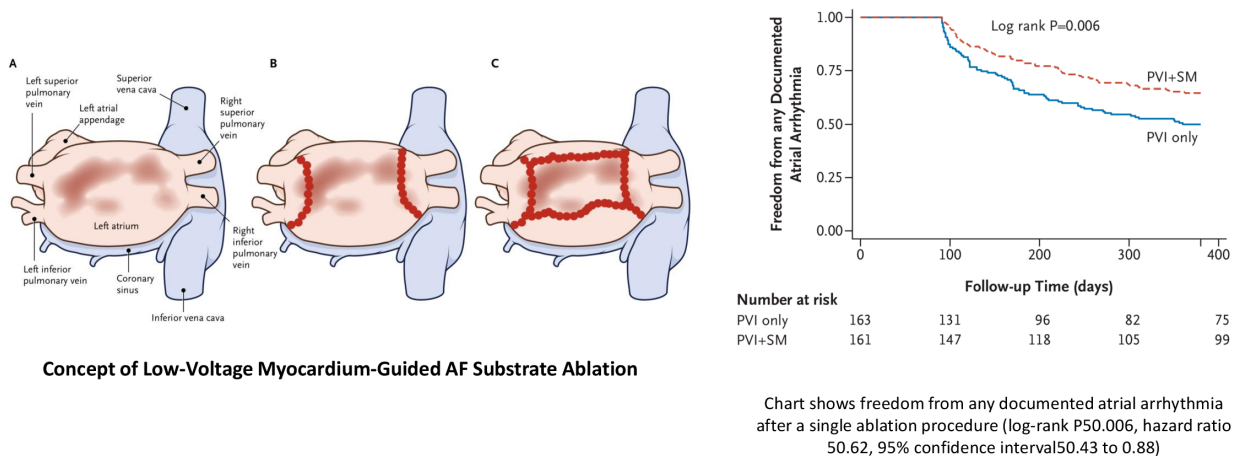


Figure 12: Clinical outcomes of randomised trial comparing pulmonary veins isolation plus voltage-guided ablation (PVI+SM) to standard ablation with PVI only and showing that PVI+SM strategy significantly improved outcomes in patients with persistent AF. From Huo Y, Gaspar T, Schönbauer R, Wójcik M, Fiedler L, Roithinger FX, Martinek M, Pürerfellner H, Kirstein B, Richter U, Ulbrich S, Mayer J, Krahnefeld O, Agdirlioglu T, Zedda A, Piorkowski J, Piorkowski C. Low-Voltage Myocardium-Guided Ablation Trial of Persistent Atrial Fibrillation. NEJM Evid. 2022 Nov;1(11).

1.1.4.3. 'C' - Cardiovascular risk factors and concomitant diseases: detection and management

Cardiovascular risk-factor burden and comorbidities, including life-style factors (obesity, sleep apnea syndrome, diabetes, hypertension, alcohol consumption, sedentary lifestyle) and borderline conditions, significantly affect the lifetime risk for AF development. (47, 75) The continuum of unhealthy lifestyle, risk factor(s), and cardiovascular disease can contribute to atrial remodeling/cardiomyopathy and development of AF that commonly results from a combined effect of multiple interacting factors (often without specific threshold values). The 'C' component of the ABC pathway includes identification and management of concomitant diseases, cardiometabolic risk factors, and unhealthy lifestyle factors. Management of risk factors and cardiovascular disease complements stroke prevention and reduces AFB and symptom severity. In the RACE 3 trial, for example, targeted therapy of underlying conditions significantly improves maintenance of sinus rhythm in patients with persistent AF and HF (97).

1.2. AF physiopathology (from Coumel Triangle to Atrial cardiomyopathy)

1.2.1. The Coumel Triangle

The pathophysiology of AF is complex.

A general overview is provided with a schematic representation of AF pathophysiology - the so-called Coumel's triangle concept.

Coumel and co-workers introduced this triangular concept that simplified interaction between the 3 classical factors that produce arrhythmia: substrate, modulating factors, and triggering factors (see figure 13).

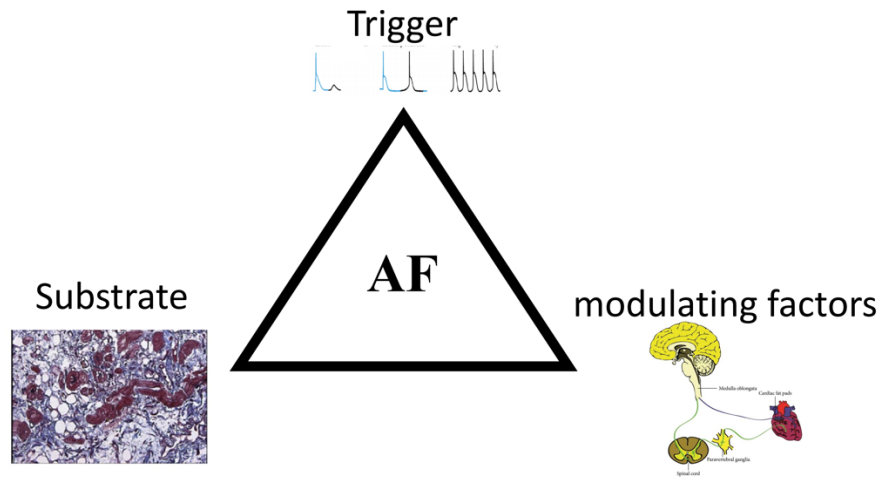


Figure 13: Coumel's triangle of arrhythmogenesis.

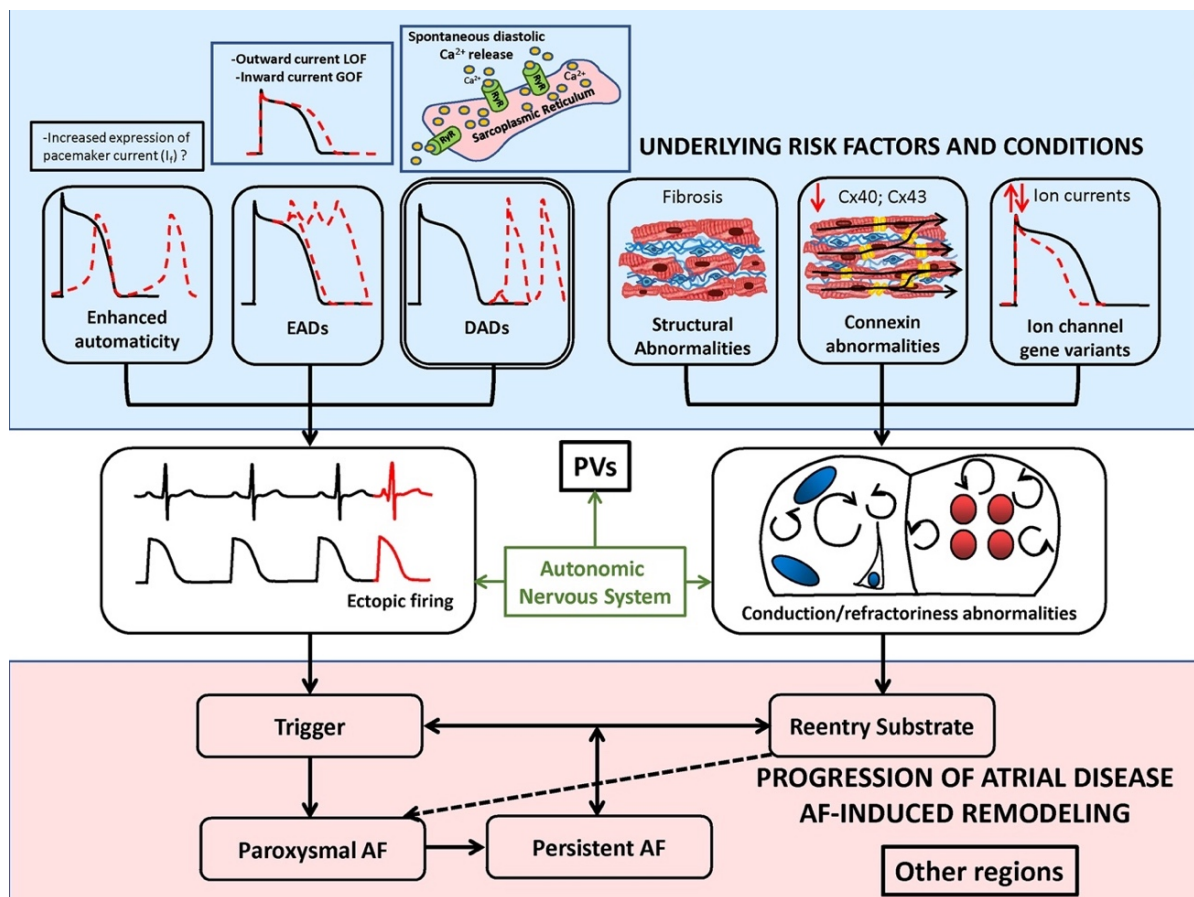


Figure 14: Overview of mechanisms linked to AF occurrence. From Nattel S. et al. *Circ Res.* 2020 Jun 19;127(1):51-72.

1.2.1.1. Triggering factors:

Ectopic activities represent spontaneous depolarizations of atrial tissue outside the sinoatrial node at rates faster than the sinus rhythm. Ectopic activities commonly (90%) originate from the PVs. (81) AF can be maintained by a rapidly firing focus, by complex multiple-circuit re-entry, or by ≥ 1 discrete rotors. (98) Ectopic atrial activities are thought to arise via triggered activity, most typically caused by delayed afterdepolarizations (DADs), (99) but in some cases by early afterdepolarizations. (100) Ca^{2+} -handling abnormalities are central to DADs and can also contribute to early afterdepolarizations (101), particularly in the presence of sympathovagal activation. (100) The underlying experimentally ascertained molecular mechanisms of these ectopic activities include intracellular Ca^{+} concentration modification mediated from sarcoplasmic reticulum Ca^{2+} -stores via leaky ryanodine receptor 2 (RyR2) and Ca^{2+} entry via L-type Ca channels (ICaL), together with a smaller Ca^{2+} influx via the sodium–potassium exchanger NCX (101, 102) (see figure 14).

1.2.1.2. Modulating factors

The important role of the diverse modulating factors from cardiovascular comorbidities to inflammation or cancer is undisputable but still far from being fully elucidated. (103) Most of the time, these factors promote AF through the autonomic nervous system or electrolyte disturbances. It is well established that the heart is richly innervated by the autonomic nervous system that can be located either inside the heart (intrinsic ANS) or in brainstem and cardiac preganglionic fibers (extrinsic ANS). Both intrinsic and extrinsic ANS divisions are fundamental for cardiac function and arrhythmogenesis. (104) Cardiac autonomic neurotransmission with adrenergic and cholinergic molecular pathways and interplay between ANS and cardiomyocytes action potential are two biomolecular explanations of the autonomic nervous system role in Coumel's Triangle (104) For example, Altered autonomic function can promote arrhythmia by vagally mediated action potential duration shortening, by adrenergically mediated Ca^{2+} loading and DAD promotion, or early afterdepolarization induction through combined sympathoadrenal discharge (107).

1.2.1.3. The atrial substrate:

The abnormal atrial substrate and its adjacent structures plays a key role in the perpetuation of AF. The modifications of this substrate come in different successive stages:

- **The electrical remodeling.** Early studies of animal models have demonstrated that AF promotes acute electrical remodeling, which in turn leads to further AF, thereby introducing the concept that 'AF begets AF'.(99) In response to either induced AF or rapid atrial pacing, a reduction in the atrial effective refractory period (ERP) occurs with an increase in the spatial heterogeneity of ERP and loss of normal ERP rate adaptation, all resulting in progressively longer durations of AF (105). AF requires specific conditions for initiation and maintenance and is favored by brief refractoriness, slow conduction, and conduction barriers that can stabilize re-entry circuits (99,106).

- **The structural remodeling.** Structural remodeling, consisting primarily of atrial fibrosis, causes this specific condition with an increase of the number of fibroblasts and in altering their properties, promoting AF by altering the electrophysiological behavior of cardiomyocytes coupled to fibroblasts through cardiomyocyte–fibroblast interactions and creating a vulnerable reentrant substrate. (101, 107) The latter can be caused by abbreviated ERP (e.g. due to a gain of function K⁺-channel mutation or to enhanced vagal tone) or by conduction abnormalities due to tissue fibrosis, connexin (Cx40 and Cx 43) dysfunction or loss of function Na⁺-channel mutations. (101) The molecular pathways involved in these structural remodeling includes defective proteostasis, activation of stress signaling, genome instability with DNA repair and mitochondrial dysfunction and inflammatory signaling (102). This point will be developed later.

- **The mechanical remodeling.** This third stage is partly the consequence of the electrical and structural remodeling. Evidence from studies consistently demonstrates that conduction slowing, conduction block, increased frequency of AF, LA dilatation, (108,

109) atrial stretch related to loss of atrioventricular synchrony (110) decrease the parameters of atrial contractile function.

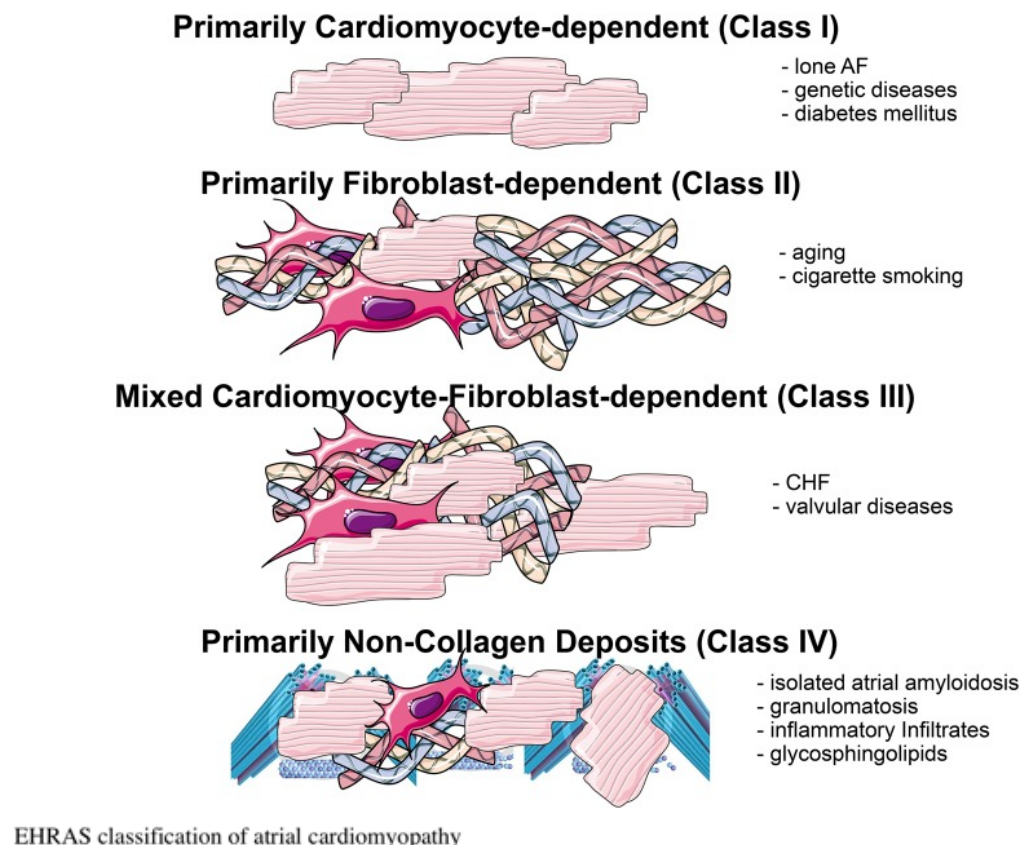
Reverse Remodeling - myth or reality ?

In summary, atrial remodeling is a time-dependent response of cardiac myocytes to varying “stressors” including electrical, mechanical, and metabolic stressors has been attributed to a variety of pathophysiologic processes. Acute atrial remodeling that occurs within 1 week of exposure to stressors is often reversible. (111, 112) In contrast, alterations that occur over the longer term (months) are usually irreversible and both risk factor management with rhythm control strategy does not appear to slow progression or promote reverse remodeling of the atrial substrate in AF. (113) In the literature, the data are mixed: in humans, AF ablation did not result in reverse remodelling at 6 months, with some evidence of further progression. (114) Studies of risk factor management have indicated a significant propensity for reverse remodeling in animal studies.

1.2.2. Atrial cardiomyopathy and atrial failure

For several years and thanks to a better understanding of the pathophysiological processes of AF and thromboembolic events, the concept of atrial remodeling has evolved towards a more global entity, the atrial cardiomyopathy. In 1997, Zipes (115) first used the term “atrial myopathy” to describe that AF can lead to myopathy through atrial remodeling. The past 2 decades have seen the concept of atrial myopathy evolving. In 2012, some experts believed that in many patients, atrial fibrosis comes from a specific disease that we called “fibrotic atrial cardiomyopathy” and that represents the genetic aspect of the arrhythmia AF. (116) Several studies have demonstrated that the relationship between AF and atrial myopathy is more complex. For example, atrial myopathy may exist without AF and can facilitate the development of AF. (116) AF is not only a risk factor for but also a marker of atrial cardiomyopathy, which could explain the lack of temporal relationship between detected AF and stroke. Currently, the latest ESC guidelines highlight that the important progress in understanding AF mechanisms and thrombogenicity reconsiders the role of atrial

cardiomyopathy (i.e. atrial structural, architectural, contractile, or electrophysiological changes with potentially relevant clinical manifestations). (47) Finally, in 2016, an EHRA/HRS/APHRS/SOLAECE expert consensus proposes a definition of atrial cardiomyopathy: ‘Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations’ and proposed a working histological/pathophysiological classification scheme for atrial cardiomyopathies: the EHRAS classification of atrial cardiomyopathy (117) (see figure 15).



EHRAS classification of atrial cardiomyopathy

EHRAS	Histological characterization class
I ^{11-15,503}	Morphological or molecular changes affecting 'primarily' the cardiomyocytes in terms of cell hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II ^{8,12,14,504-506}	Predominantly fibrotic changes; cardiomyocytes show normal appearance
III ^{9,11,12,217,266}	Combination of cardiomyocyte changes (e.g. cell hypertrophy, myocytolysis) and fibrotic changes
IV ¹⁷⁻¹⁹	Alteration of interstitial matrix without prominent collagen fibre accumulation
IVa	Accumulation of amyloid
IVf	Fatty infiltration
IVi	Inflammatory cells
IVo	Other interstitial alterations

Figure 15: Histological and pathophysiological classification of atrial cardiomyopathies (EHRA/HRS/APHRS/SOLAECE): EHRAS classification. From EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies. *Europace*. 2016 Oct;18(10):1455-1490.

The diagnostic algorithm for atrial cardiomyopathy should follow a stepwise approach, identifying risk factors for atrial cardiomyopathy, atrial electrical and mechanical dysfunction and increased thrombotic risk (see figure 16). Accordingly, the arrhythmogenic remodeling of the atria has been associated to the perpetuation of AF and the recent ESC guidelines recommend (recommendation class IIA, level of evidence C) its evaluation in all AF patients to optimal management. (47)

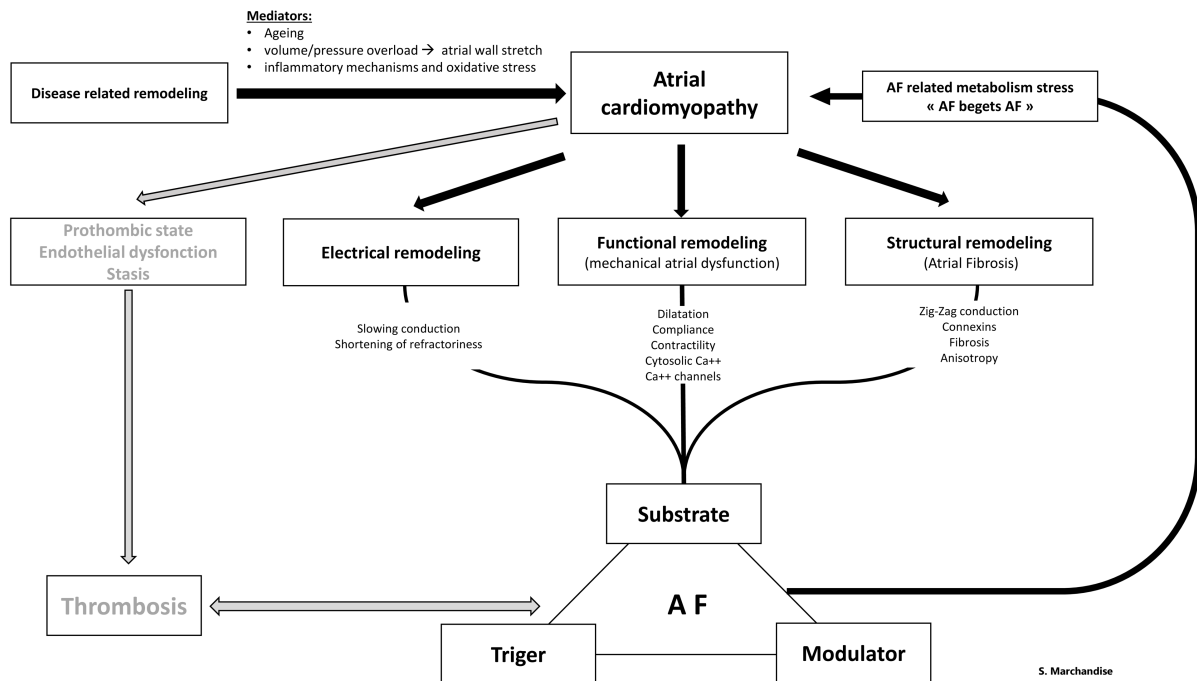


Figure 16: Atrial cardiomyopathy: its Relationship between contributing factors, atrial fibrillation and thromboembolic events. AF: Atrial Fibrillation.

Summary of the imaging diagnostic modalities available in clinical practice to detect and evaluate left atrial structural remodeling and atrial cardiomyopathies

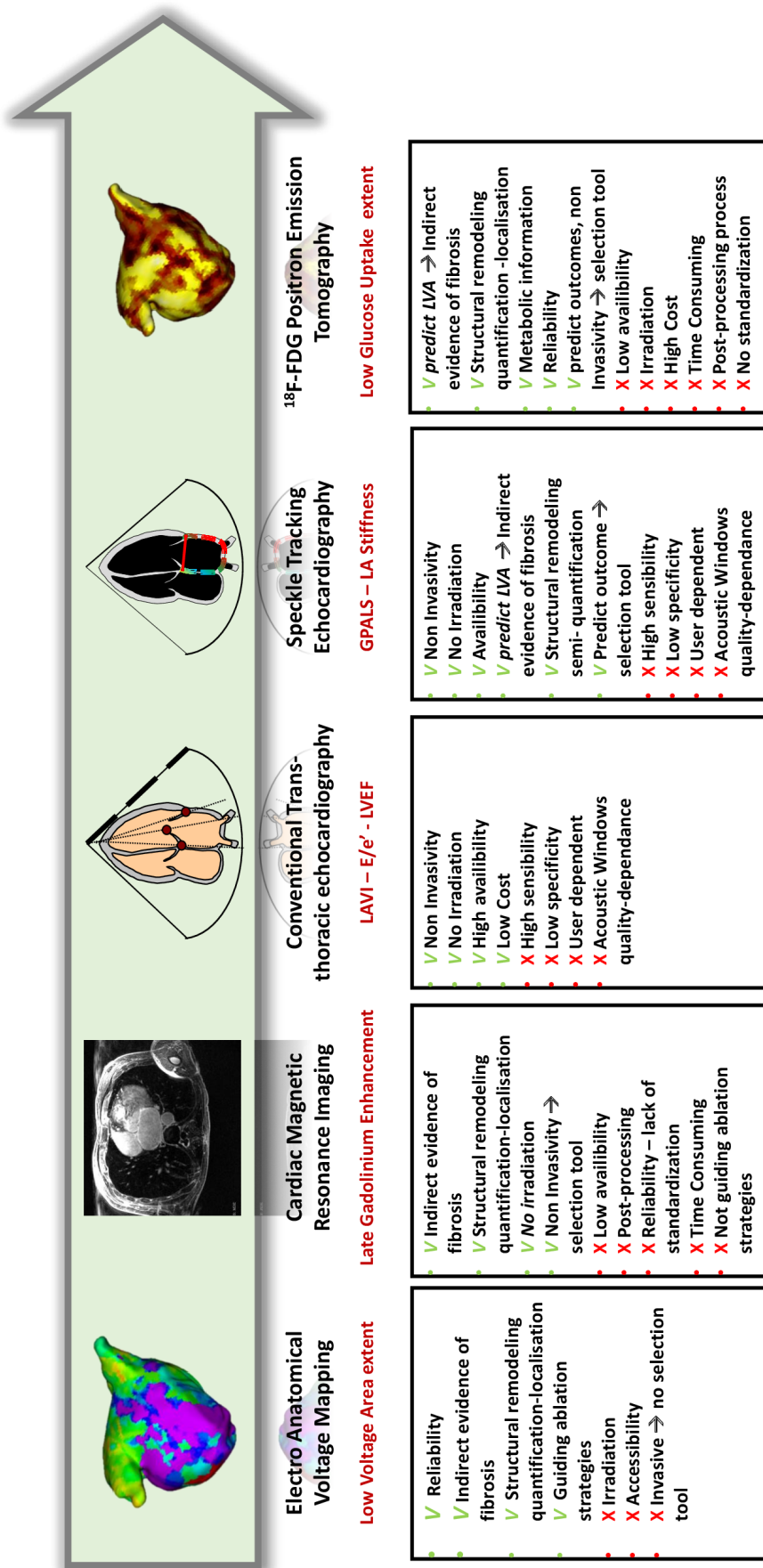


Figure 17: summary of several imaging diagnostic modalities available in clinical practice to detect and evaluate atrial cardiomyopathies and left atrial structural remodeling with advantages (V: green affirmation), limitations and pitfalls (X: red affirmation). EAVM: electroanatomical voltage mapping, cMRI: cardiac magnetic resonance imaging, TTE: trans thoracic echocardiography, STE: speckle tracking echocardiography, ¹⁸F-FDG-PET ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography.

1.2.3. Imaging techniques to detect and evaluate atrial cardiomyopathies and left atrial structural remodeling

Macroscopically, atrial cardiomyopathy may manifest as AF or non-AF atrial arrhythmias, atrial dilatation, impaired atrial systole, or abnormal cardiac imaging findings with areas of fibrosis. (115) Various imaging modalities (including electroanatomic voltage mapping, cardiac magnetic resonance imaging, conventional echocardiography, speckle tracking echography and positron emission tomography) have been investigated to establish the diagnosis of left atrial cardiomyopathy. All imaging techniques have advantages, limitations and pitfalls (see figure 17). To date, there are no universally accepted recommendations to evaluate structural remodeling. A multimodal approach is sometimes required.

1.2.3.1. Echocardiography:

Two-dimensional echocardiography, pulsed-wave Doppler, speckle-tracking echography (strain and strain rate imaging) are useful to provide volumetric and functional assessment of the LA. (118, 119) Larger LA size, assessed by echocardiography, is associated with a higher recurrence rate of AF after ablation procedure (120), and with an increased risk of recurrent stroke in patients with nonvalvular AF and ischemic stroke (121). However, conventional echocardiography presents low sensitivity as small amounts of fibrosis may be missed. Also other echocardiographic parameters such as LAVI obtained by 3D TTE, left atrial stiffness, or LA contractile dysfunction evaluated through speckle tracking echography and longitudinal strain have been proposed and represent a non-invasive approach to evaluate atrial structural remodeling and atrial cardiomyopathy. Indeed, left atrial strain and strain rate were found to correlate with LA fibrosis by LGE-cMR (122) and to be associated with the risk of AF and stroke. STE LA strain was also shown to predict the recurrence of atrial arrhythmias after catheter ablation or electrical cardioversion (123–128). Most of these studies evaluated STE, while patients were in sinus rhythm. Recently, our team showed that STE could predict the severity of atrial fibrosis and the success of AF catheter ablation procedures in patients during persistent AF (129).

Advantages, limitations and pitfalls of echocardiography. Transthoracic echocardiography is a critical tool in the field of clinical cardiology. It is the first-line imaging modalities in the evaluation of cardiac disease owing to its low cost, portability, widespread availability, lack of ionizing radiation, and ability to evaluate both anatomy and function of the heart. However, ultrasound is a user-dependent modality who influence inter and intraobserver variability. Moreover, some views may be difficult to acquire due to respiration interference, anatomical variant of the chest cavity or atypical clinical situation. (130) Finally, this imaging technique does not allow a quantitative analysis of the LA structural remodeling extent.

1.2.3.2. Cardiac magnetic resonance

In the last decades cardiac magnetic resonance (cMR) has had an increasingly important role as a research tool to investigate the pathological substrate of AF and has become the gold standard of assessment of chamber structure and function, mainly because of its superiority in tissue characterization, particularly in fibrosis (131).

Since 2009, cMR imaging with the late enhancement of gadolinium (LGE) has been used as a non-invasive and non-ionizing radiation technique to detect atrial fibrosis (132). Moreover, the DECAAF study showed that using a scoring system (Utah score) for the area of delayed enhancement, the extent of fibrosis evaluated by LGE cMR predicted the outcome of AF ablation. The risk of recurrent AF increased from 15% for stage I fibrosis (<10% of the atrial wall) to 69% for stage IV fibrosis ($\geq 30\%$ of the atrial wall). The authors suggested that cMR quantification of fibrosis may play a role in the appropriate selection of patients most likely to benefit from AF ablation. (133) (see figure 18) Interestingly, a validated assessment of pericardial fat volume by cMR has been shown to be predictive of the presence and chronicity of AF and the effectiveness of ablation procedure. (134, 135) These findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat on the arrhythmogenic substrate supporting AF (134).

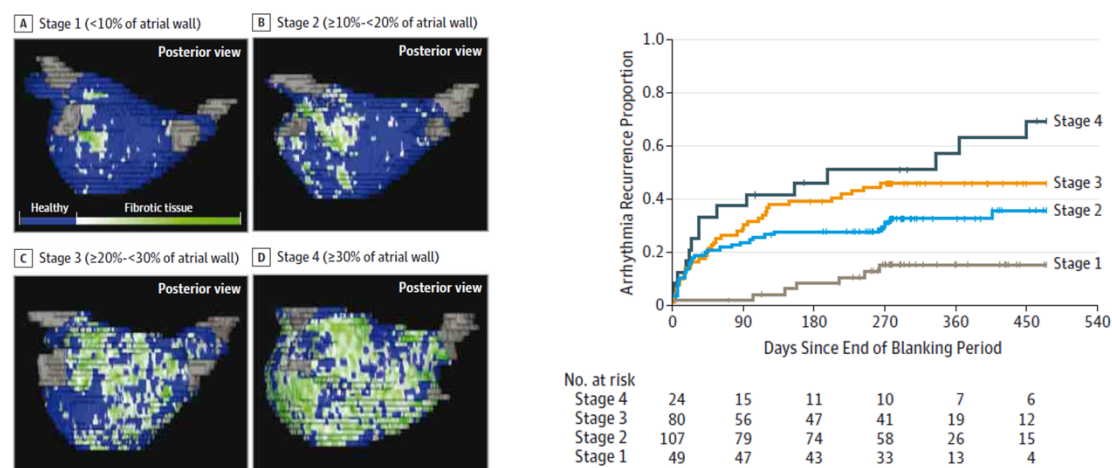
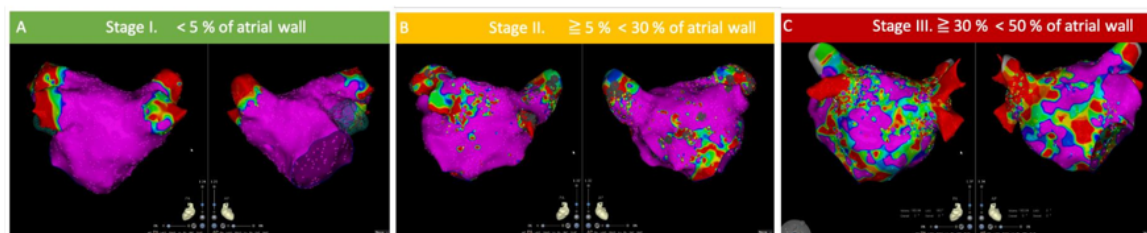
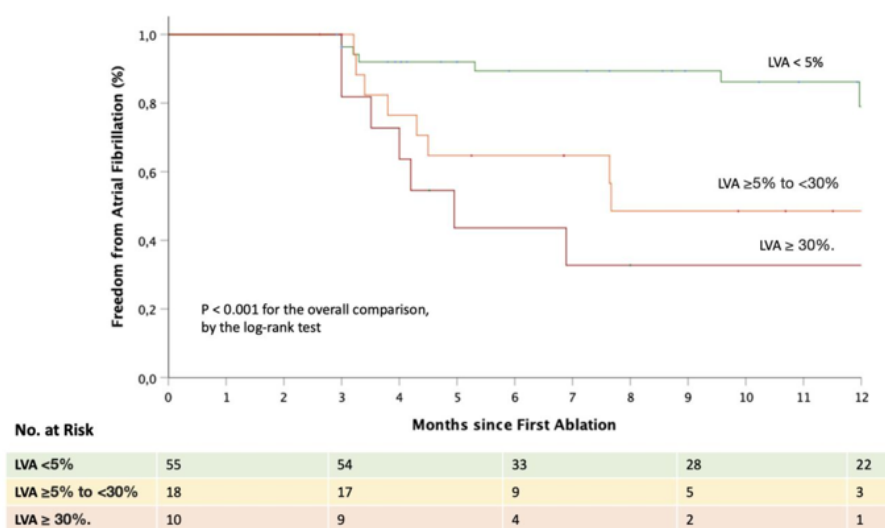


Figure 18: Among patients with AF undergoing catheter ablation, atrial tissue fibrosis estimated by delayed enhancement MRI was independently associated with likelihood of recurrent arrhythmia. From Marrouche N et al. The DECAAF study. JAMA. 2014 Feb 5;311(5):498-506.

However, several limitations must be addressed to cMR: these techniques require time and specialized post-imaging processing. Accurate 3-dimensional imaging of the LA involves manual segmentation from other images and careful intensity threshold calibration to differentiate normal from fibrotic tissue. There is debate of the optimal image intensity ratio to define scar. Threshold varying between 2-4 SD over mean of normal myocardium have been proposed by some authors, while other groups used the blood pool as reference to identify LA fibrosis. (136) While they are commonly used for ventricular imaging, they have not been widely employed for atrial imaging because of the technical challenges in achieving adequate image resolution and segmentation in the thin-walled atrium. (117) Moreover, the limited availability of cMR, its high cost, claustrophobic patients, suboptimal image quality during arrhythmia, respiratory artefact and relative contraindication for patients with medical devices such as abandoned pacemaker leads, are barriers to its widespread clinical use. (115, 117, 136) Finally, the DECAAF II trial did not find added value in terms of AF recurrence with a LGE-cMR-guided ablation strategy, confirming the difficulty of developing a tailored approach based on identification of the arrhythmic substrate with non-invasive imaging tools (131, 137).



Three stages of left atrial (LA) low-voltage area (LVA).
The color gradient indicates serial changes in the electrogram amplitude from pink at >0.5 mV to red at <0.1 mV



Kaplan-Meier estimates of freedom from documented persistent atrial fibrillation.
Comparison between high-density bipolar voltage map with different stage of Low Voltage Area (LVA).

BeHRA-MYLAN Abstract poster was won by
Dr Sébastien Marchandise,
Cliniques Universitaires Saint-Luc -
UCLouvain
Impact of Low Voltage Area extend
assessed during a persistent Atrial
Fibrillation ablation
procedure on AF recurrence
Congratulations!

Figure 19: Impact of LVA extent assessed during a persistent AF ablation procedure on AF recurrence. LVA: low voltage area. AF: Atrial Fibrillation. From Sébastien Marchandise et al. BHRM congress best abstract award 2020.

1.2.3.3. Electroanatomical voltage mapping

An increasing variety of approaches are available to map AF. Despite differences in how signals are recorded and analysed, most clinical systems reveal organized features in AF in both atria where ablation can acutely impact AF in patient subsets. (138) In patients undergoing AF ablation procedures, electroanatomical voltage mapping (EAVM) system combine anatomical and electrical information by catheter sequential point-by-point or simultaneous multielectrode mapping, allowing an accurate anatomical reconstruction of the 3D shell of the targeted cardiac chamber. Moreover, this 3D electroanatomical voltage mapping can help identify low-voltage areas (LVAs), slowed conduction and complex fractionated arial electrogram (CFAE) that may represent areas of structural change – the hallmark of fibrosis. (139, 151, 168). The use of 3D mapping systems has been demonstrated to reduce fluoroscopy exposure, procedure times and total ablation time. (140) However, several works showed other clinical benefit of EAVM systems. Studies have shown that patients with persistent AF have a higher extent of LVAs compared with those with paroxysmal AF (141) and that this extent is an independent predictor for recurrence event after AF ablation procedure. (142, 143) This was confirmed by our data (presented as oral abstract in 2020 at the Belgian Heart Rhythm Meeting): Between March 2017 and December 2019, we retrospectively studied 83 patients with persistent non valvular AF undergoing PVI in our center. Subjects underwent voltage mapping with the Carto system and were followed-up with a clinical evaluation at 2, 6, 12, 18 and 24 months and 24 hours Holter monitoring within one year of ablation. After 18 months mean follow-up, 58 % of our population was free from recurrent AF. The LVA extent was low in 55 patients (66%), moderate in 18 (22%) and important in 10 (12%) patients. After 12 months, AF recurrence free survival rates were respectively 80%, 53%, and 27% in patients with low, moderate, and important LVA, (log-rank, $p < 0.001$) (see figure 19). The difference was significant between the 3 LVA extent stages. Cox univariate analysis identified only age (HR 1.05 95%CI [1.00;1.10], $p = 0.04$) and LVA (HR 4.0 [1.6;9.9], $p < 0.001$) as predictors of AF recurrence free survival. In multivariate analysis LVA remained the sole predictor of AF recurrence. This confirm that LVA extent is the strongest independent predictor of AF recurrence in persistent AF and the importance of pre-procedural evaluation of LA fibrosis to predict success of AF ablation procedure (143).

Moreover, several other groups reported that use of these mapping systems with or without image integration improves the safety and efficacy of AF ablation. (144, 145) Furthermore, these LVAs can be directly targeted with radiofrequency ablation to perform substrate modification. This tailored and therapeutic approaches targeting atrial fibrosis has been reported to improve ablation success rates in persistent AF patient (95, 146-148). Obviously, the use of 3D mapping systems will increase the cost of the procedure. This imaging modality is an invasive tool, generating ionizing radiation only available at the time of ablation and is not of value for the selection of catheter ablation candidates (51, 129, 138).

Finally, voltage mapping can be performed in patients both in sinus rhythm or during arrhythmia. (149) But, it is important to note that bipolar voltage amplitudes, distribution and extent of LVAs on 3D mapping systems are critically dependent on multiple parameters: the rhythm during acquisition, electrodes orientation relative to direction of wavefront (activation vector and angle of incidence) (150), recording electrode size, interelectrode spacing, tissue contact and atrial wall thickness, filtering, mapping density, mapping resolution. All these variables are key determinant of recorded bipolar voltage and may provide a different evaluation of underlying atrial substrate. (152-154, 158). Finally, there are different definitions of LVA in the literature:

- traditional and historical definition (silent areas (scar): absence of recordable activity or a bipolar voltage amplitude ≤ 0.05 mV; LVA contiguous areas of bipolar voltage ≤ 0.5 mV in sinus rhythm (155) corresponding to ≤ 0.31 mV during AF (156).
- Electrophysiological and histological definition: LVA as 0.1-0.4 mV and transitional zone as 0.4-1.3 mV (157). Accordingly, the definition of LVA is still controversial (158).

1.2.3.4. Positron emission tomography with ^{18}F -FDG.

Positron emission tomography (PET) with ^{18}F -fluoro-desoxyglucose (^{18}F -FDG) is the gold standard for metabolic evaluation of the left ventricle (LV). Different protocols are available using metabolism tracers to acquire images for specific dataset including viability imaging or inflammation process such as cardiac sarcoidosis or endocarditis (159). The interest of PET in the field of AF to evaluate atrial cardiomyopathy is emerging with different protocols. Yet FDG uptake of the heart is critically influenced by metabolic conditions. Retrospective and

prospective works have studied FDG uptake with strategy to suppress physiological myocardial FDG uptake by prolonged fasting, dietary manipulation, and heparin loading and shown that the FDG uptake was related to the increased activity of atrial structures and epicardial adipose tissue (EAT) and inversely correlated with LA fibrosis (160-163). However, according to partial volume effect (PVE) and thin atrial wall, the interpretation of FDG uptake is complex and, in these studies, in the absence of histological confirmation it was impossible to know whether the atrial FDG activity measured corresponds to the metabolic activity in atrial wall, in the EAT or both (164). In our work, we tried to elucidate that question by evaluating the glucose metabolism through ^{18}F -FDG PET/CT in the process of atrial remodeling in patients with persistent AF with similar preparation used to evaluate myocardial viability in coronary patients with a nicotinic acid derivative (Acipimox) after overnight fasting to maximally stimulate myocardial glucose uptake (figure 20). PET is a technology that requires rigor to allow precise quantification of the tracer fixed in a specific region of interest. Fixations are often expressed in standardized uptake value (SUV) which constitutes the quantitative index most used in clinical practice. The radioactive concentration is expressed in kBq/mL. This activity is corrected for the patient's morphology according to body surface area (SUV_{bsa}) or body weight (SUV_{bw}). The calculation of the standardized uptake value (SUV) corrected for body weight therefore corresponds to the following formula:

$$\text{SUV}_{\text{bw}} = \frac{\text{Radiopharmaceutical concentration (fixation) (Bq/mL)}}{\text{Injected activity(Bq)/Body Weight(kg)}}$$

However, PET has several disadvantages and limits. First, this noninvasive imaging modality generating not negligible ionizing radiation. Then, nuclear medicine procedures can be time-consuming, require specialized post-imaging processing and availability (PET can be done only if the radionuclide is produced at a nearby location and can be obtained quickly). Moreover, partial volume effect (consequence of limited spatial resolution) leading to quantitative underestimation of tracer uptake in reconstructed images, artifacts generation (respiratory motion is the most common) and reliability of the results which depend on rigorous preparation and blood sugar or blood insulin levels, are all criticisms that must be addressed to this technique (164).

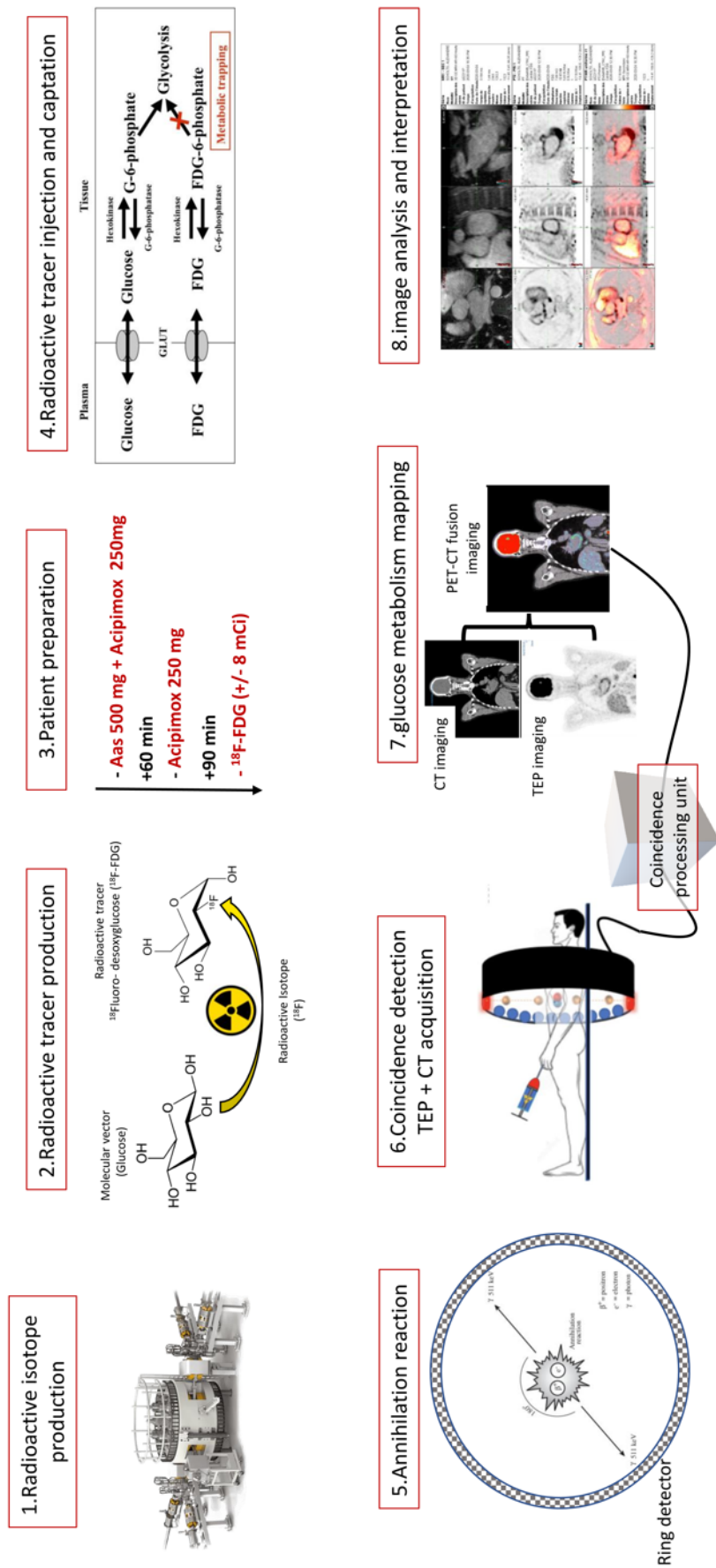


Figure 20: Workflow of ^{18}F FDG-PET images acquisition during TRIATLON project. Step 1 and 2: local radioactive isotope production. Step 3: patient preparation with overnight fasting and received a nicotinic acid derivative (Acipimox 250 mg) to maximally stimulate myocardial glucose uptake. Step 4: radioactive tracer injection and cardiomyocyte uptake. Step 5 and 6 : Annihilation reaction then coincidence detection TEP + CT acquisition. Step 7: glucose metabolism mapping after coincidence processing unit analysis. Step 8: image analysis and interpretation with MIM software.

1.3. Nature and Role of Structural Remodeling and Atrial cardiomyopathy

The pathogenesis of the myocardial damage in AF is multifactorial with different mechanisms superimposing one on another. These factors contribute differently depending on the main underlying cause of AF.

As already mentioned above, certain cardiac disease and risk factors (i.e. age, obesity, HTA, HF, structural heart disease, sleep apnea or alcohol intake) are associated with AF, likely through both different and interacting mechanisms like (51, 102, 165)

- atrial tachycardia, with a high rate of cell depolarization leading to metabolism stress,
- volume/pressure overload leading to increasing atrial wall stretch,
- inflammatory mechanisms and oxidative stress,

Fibroblast proliferation and extracellular matrix deposition is the consequence of these aggressions and predispose to anisotropy and re-entry (166). The electrical derangement adds to a vicious cycle in which “AF begets AF” —rapid atrial myocyte depolarization leads to intracellular calcium accumulation, triggering adaptive and inflammatory responses that potentiate myocyte apoptosis and accelerate atrial fibrosis (115, 165).

Histologically, atrial fibrosis is characterized by cardiomyocytes exhibiting loss of sarcomeres as well as accumulation of glycogen storage granules, which are adaptive alterations in cellular metabolism not unlike those observed in response to ischemia (165, 167).

Recently, histological validation of atrial structural remodeling was performed with EAVM. This study confirm histological correlates of atrial structural remodelling were fibrosis, increased intercellular space, myofibrillar loss, and decreased nuclear density (168).

Molecular pathways involved in these structural remodeling include defective proteostasis, activation of stress signaling, genome instability with DNA repair and mitochondrial dysfunction and inflammatory signaling (102).

In this project, we focused on the metabolism stress induced by a high rate of cellular depolarization during AFib, its consequences on energy substrates and the way to highlight it.

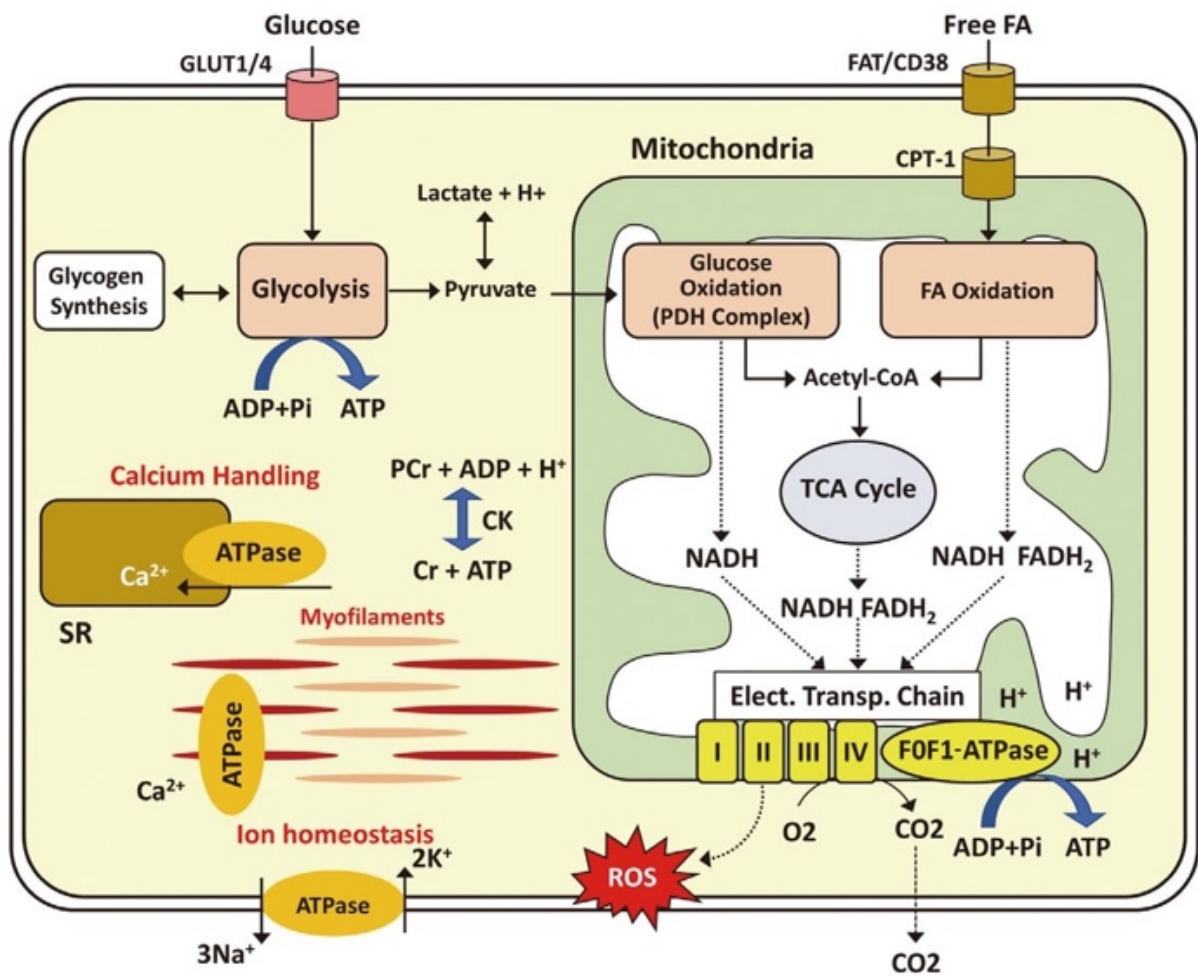


Figure 21: Energy production system and utilization in cardiomyocytes. From Harada M et al. *Circ J.* 2017 Nov 24;81(12):1749-1757.

1.3.1. Cardiomyocyte energy metabolism during sinus rhythm

Excitation–contraction coupling in cardiac myocytes requires high amounts of energy. Adenosine triphosphate (ATP) is this essential energy source for cardiac work and is produced by the metabolism of several energetic substrates, including fatty acids, glucose, amino acids, and ketone bodies. Fatty acids (FA) and glucose are the principal energy substrates in cardiomyocytes (167).

The energy production pathways include (167, 169, 170, 171) (see figure 21).

1. Glycolysis. This anaerobic pathway generates limited ATP in the cytosol. Glucose is taken into the cell via the sarcolemma glucose-transporters types 1 and 4 (GLUT1/4).
2. Glucose oxidation. This aerobic pathway takes place into the mitochondria from the endproduct of glycolysis, the pyruvate. Pyruvate is catalyzed to produce acetyl-CoA and nicotinamide adenine dinucleotide hydrogen (NADH) by pyruvate dehydrogenase (PDH), a rate-limiting enzyme for glucose oxidation.
3. Fatty acids oxidation. This aerobic pathway takes place into the mitochondria. FA oxidation cycle produces acetyl-CoA, NADH and FADH₂. Circulating FAs enter cardiomyocytes via the FA transporter, FAT/CD36. Carnitine palmitoyl transferase-1 (CPT-1) allows FA entry into mitochondria for FA oxidation.

FA oxidation and glucose oxidation produce acetyl-CoA, and are interdependent such that increased FA oxidation suppresses glucose oxidation and vice versa (171). Acetyl-CoA is the main substrate for the tricarboxylic acid (Krebs) cycle, a series of metabolic processes that generate energy sources via oxidative reactions. Because the amount of ATP produced per O₂ consumed is greater with when glucose is oxidized compared to fatty acids, fatty acids are a less efficient energy substrate than glucose. Six O₂ are consumed and 31 ATP are produced from the full oxidation of one glucose molecule. Oxidation of one palmitate consumes 23 O₂ while only producing 105 ATP (171).

4. Electron-transport chain (ETC) metabolism. It is the final metabolic process in the inner mitochondrial membrane. The ETC requires the coordination of several enzyme: 4 enzyme complexes (designated I–IV) for redox reaction and an ATP synthase (F₀F₁-ATPase) for ATP synthetization.

Calcium (Ca²⁺) is a key regulator of mitochondrial function by stimulating the Krebs cycle, which produces nicotinamide adenine dinucleotide for ATP production at the electron transport chain and nicotinamide adenine dinucleotide phosphate for the elimination of reactive oxygen species (ROS) (169, 172).

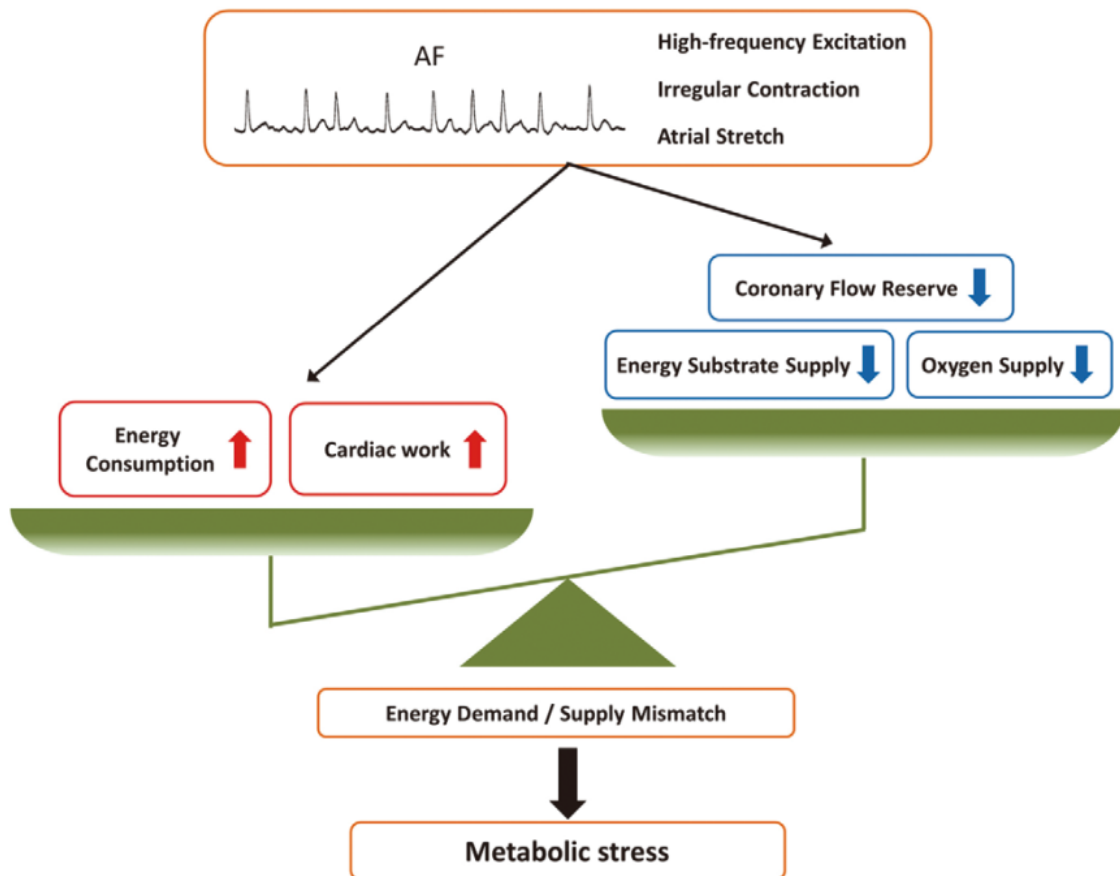


Figure 22: Metabolic imbalance and metabolic stress in atrial fibrillation. From Harada M et al. *Circ J.* 2017 Nov 24;81(12):1749-1757.

1.3.2. Cardiomyocyte energy metabolism during AF

AF is characterized by irregular high-frequency excitation and contraction at the atrial level. Due to the high stimulation frequency endured during arrhythmia, the energy consumption and therefore, energy requirement of atrial tissue is increased (171) and affect atrial energy demands, change the balance between metabolic demand and supply, resulting in metabolic stress. (see figure 22) Accordingly, a variety of studies suggest a role for relative ischemia in AF. (167)

This suggestion is firstly based on several studies conducted with animal models. Ausma and al. reported in goats, structural changes of atrial myocardium (myofilament loss, glycogen accumulation, altered mitochondrial morphology, sarcoplasmic reticulum fragmentation, and nuclear chromatin dispersion) due to sustained AF resembling hibernating myocardium. (173) Pacchia et al. highlights the effects of AF on LA perfusion and the interplay between AF, ischemia and fibrosis. (174) van Bragt et al. showed that Pigs subjected to rapid atrial pacing to mimic AF show increased atrial myocardial perfusion but also enhanced oxygen extraction. (175) This team observed also that increased venous lactate concentrations in the atrium indicate a relative ischemia. (175) Finally, Kalifa et al. showed that acute stretch-related AF induces specific modifications of atrial myocytes energetics (ATP concentrations tend to decrease) that may play a pivotal role in the perpetuation of the arrhythmia (176).

All these observations support the hypothesis in AF-related metabolic stress with an increasing metabolic need and a limited energy supply (167); and the existence of an atrial cardiomyopathy where altered atrial metabolism is a key component of both AF initiation and progression. Indeed, the metabolic wasting might lead to ischemia or hibernation process, resulting in myocyte necrosis and apoptosis and subsequent replacement of the tissue by fibrosis. However, to my knowledge, no study including AF patients directly support this paradigm.

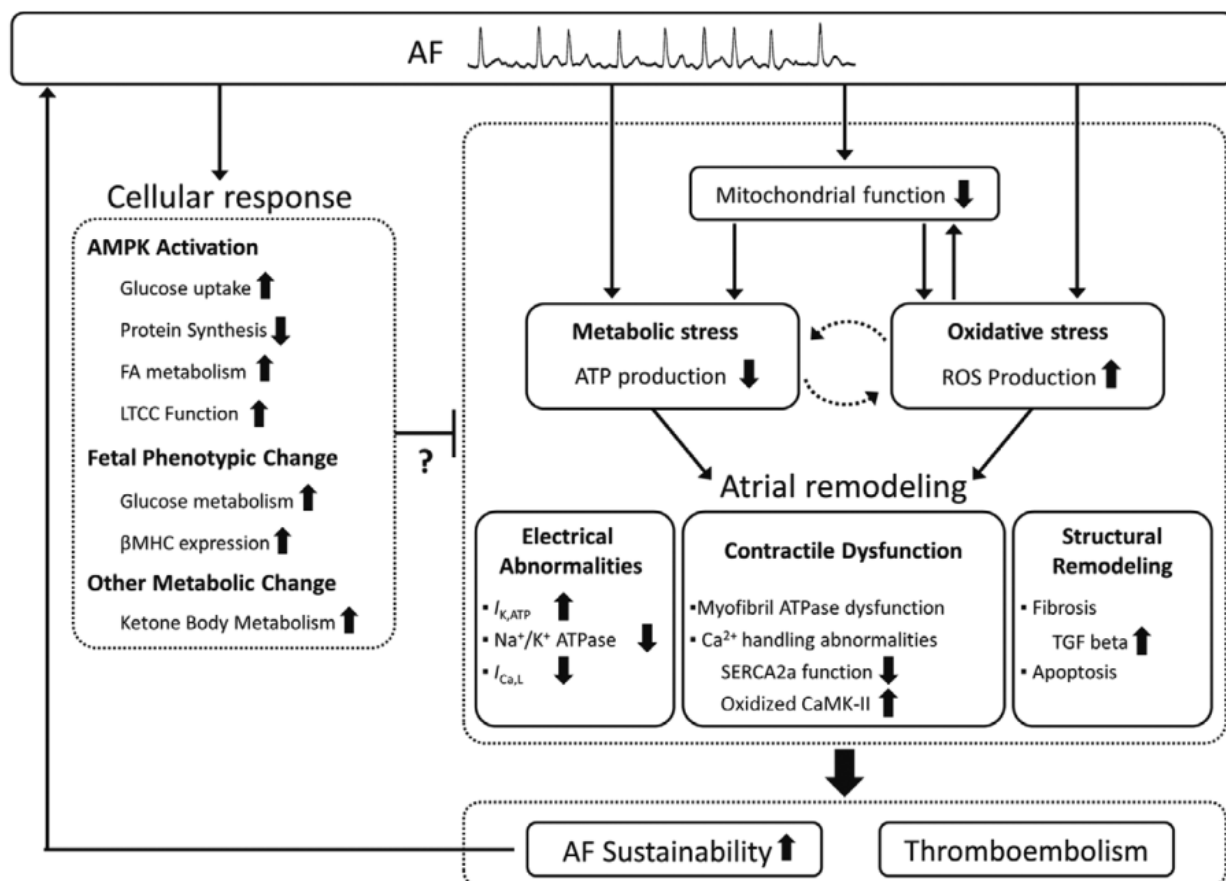


Figure 23: Contribution of energetic dysfunction to pathophysiology of atrial fibrillation. From Harada M et al. *Circ J.* 2017 Nov 24;81(12):1749-1757.

This metabolic stress is associated with a series of modifications at the cellular level: (see figure 23)

- **A metabolic shift to a more fetal phenotype (167, 177)**: During fetal development, glycolysis is a major energy source for proliferating cardiomyocytes. Oxidation becomes predominant as cardiomyocytes mature and mitochondrial oxidative capacity increases. Glucose metabolism is more energy efficient, so with pathological stresses, energy metabolism switches to a more fetal phenotype. (178) A transcriptomic study demonstrated that patients with permanent AF have more fetal phenotypes of metabolism related gene expression than patients in sinus rhythm, showing a marked increase in glycolysis-related gene expression. (177)
- **AMPK Activation**: AMP-activated protein kinase (AMPK) is an energy sensor and regulator of cellular metabolism. It is activated by metabolic stress and AF and helps maintain the intactness of atrial Ca^{2+} handling, and cell contractility. AMPK compensates for energy depletion by increasing energy production and suppressing energy consumption. AMPK activation increases the expression of GLUT1/4 and promotes its trafficking into the sarcolemma, increasing glucose uptake. (179) interestingly, some works suggest that this phenomenon dependent on the stage of AF. (180)
- **Increased utilisation of ketone bodies** has been reported in AF. (181)
- **Mitochondrial dysfunction and ROS emission**: Some teams discussed a hypothesis that increased energy demand during AF lead to oxidative stress, shifting the redox environment to a state of energy deficit and compromised ROS scavenging capacity. (169)

In summary to this introduction:

- AF is the most common rhythm disorder encountered in clinical practice and contributes to cardiovascular morbidity and mortality.
- Its persistent form remains a challenge for the clinician because its pathophysiology and its association with atrial cardiomyopathy or LA remodeling are still incompletely understood. Moreover, presently available therapies have many limitations, including limited efficacy of AF ablation procedure.
- Atrial cardiomyopathy with structural and functional atrial remodeling is a well-established hallmark involved in the development and progression of AF. It is strongly associated with the development of progressive atrial fibrosis, which will ultimately lead to AF persistence. Accordingly, an ablation strategy is increasingly moving towards a tailored approach based on the evaluation of structural atrial remodeling should be considered in all persistent AF patients to optimize management.
- Several tools exist to evaluate this arrhythmogenic remodeling. All imaging techniques have advantages, limitations, and pitfalls.
- AF is characterized by irregular high-frequency excitation and contraction that affect atrial energy demands, change the balance between metabolic demand and supply, resulting in metabolic stress, cellular metabolic changes including glucose as energy substrates in cardiomyocytes. This metabolic imbalance during AF is associated with the development of LA remodeling. Observations concerning cardiomyocyte energy metabolism suggests that AF induces a hibernating-like phenotype of the atrial cardiomyocytes and activates the AMPK signaling pathway leading to stimulation of glucose transport via Glucose Transporter Type 1 and 4 (GLUT/1,4) activation, increasing glucose uptake.
- ^{18}F -FDG PET is currently the gold standard for metabolic evaluation of the LV. In the field of AF, the interest of ^{18}F -FDG PET is emerging and the potential role that the glucose uptake evaluation may play in the pathogenesis of AF, the LA remodeling and the atrial cardiomyopathy is not yet well defined.

- CHAPTER II - AIMS OF THE THESIS -

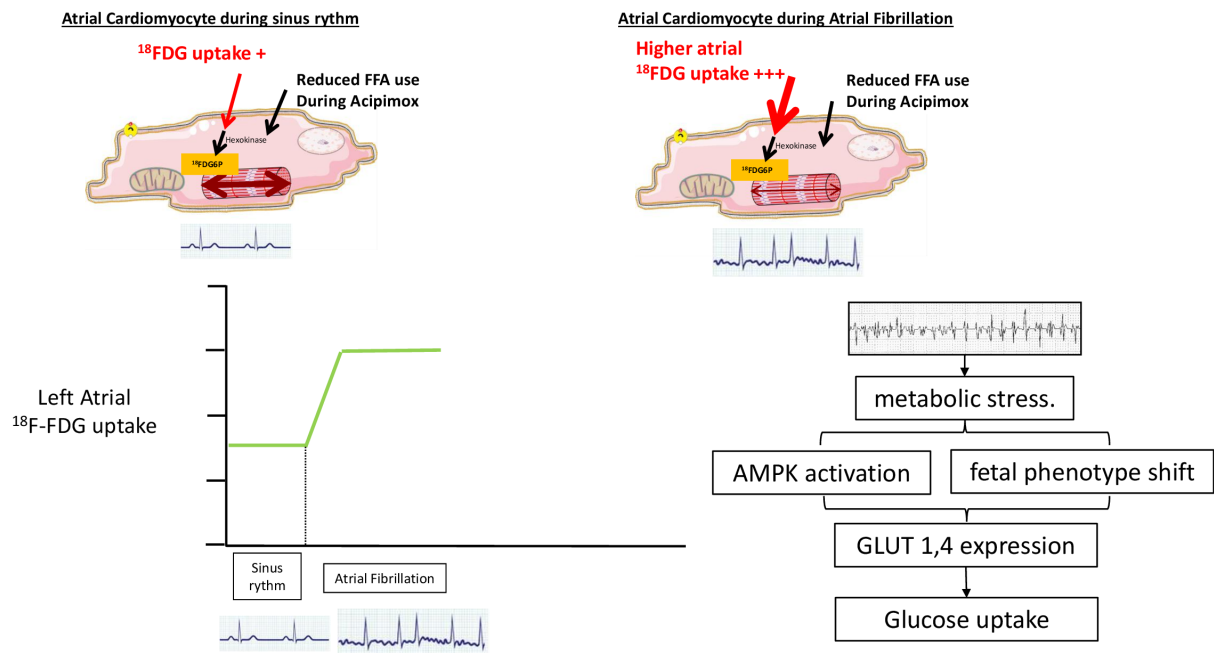


Figure 24: illustration of our hypotheses with evolution of LA glucose uptake by ^{18}F -FDG PET according to rhythm status. LA: Left Atrial, ^{18}F -FDG: ^{18}F FluoroDesoxyGlucose.

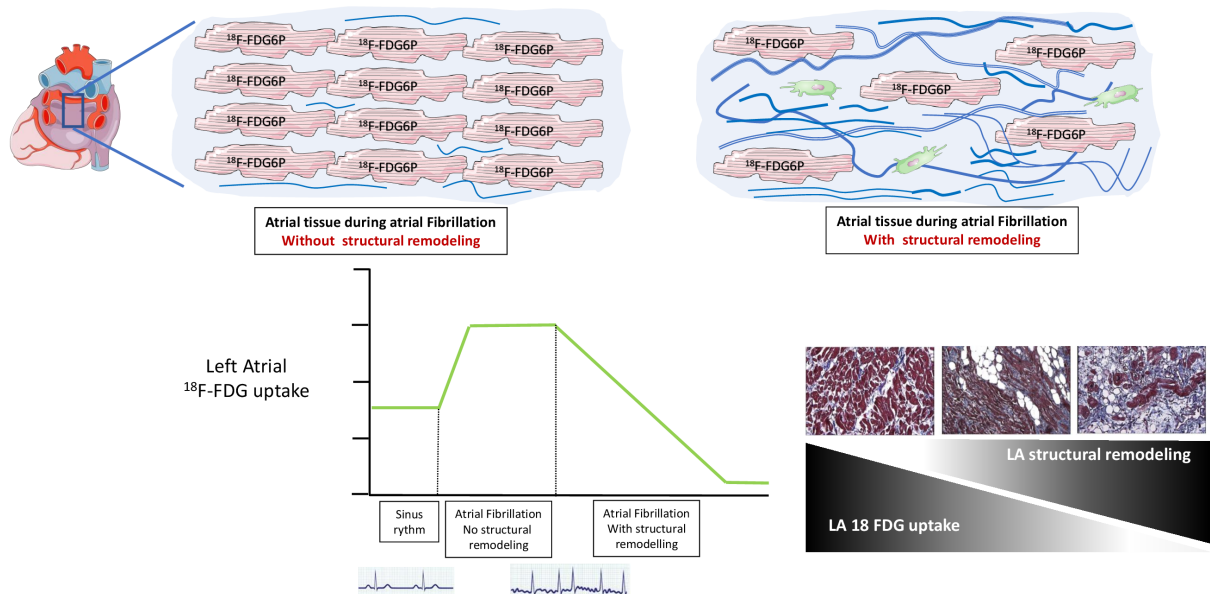


Figure 25: illustration of our hypothesis with evolution of LA glucose uptake by ^{18}F -FDG PET according to rhythm status and LA structural remodeling extent. LA: Left Atrial, ^{18}F -FDG: ^{18}F FluoroDesoxyGlucose.

2. CHAPTER II - AIMS OF THE THESIS

Hypothesis

According to this introduction, in line with the observations concerning cardiomyocyte energy metabolism during AF, the LA structural remodeling composition and the background of ^{18}F -FDG PET, we formulated our hypotheses: (see figure 24, 25)

- During AF, glucose uptake by LA cardiomyocytes could be increased. Using the ^{18}F -FDG as a marker for glucose uptake, ^{18}F -FDG uptake quantify by ^{18}F -FDG-PET in persistent atrial fibrillation patient could be increased (see figure 24).
- The uptake delta between AF and sinus rhythm could reflect a metabolic shift in the use of energy substrates by the cardiomyocyte (see figure 24).
- A reliable quantification and localization of low glucose uptake area by a three-dimensional quantitative LA map with ^{18}F -FDG PET could correspond to fibrosis extent and lead to evaluating atrial structural remodeling associated with persistent AF (see figure 25).
- A comparison between ^{18}F -FDG PET and other imaging modalities (EAVM, LGE cMR or TTE) could confirm the interest of PET to quantify fibrosis, assess atrial cardiomyopathy/LA structural remodeling and help improve the management of patients with persistent AF.

To answer our hypothesis, we started the multidisciplinary TRIATLON (Atrial Perfusion - Metabolism and Fibrosis in Atrial Fibrillation) project with the following main objectives:

1. To evaluate the effect of different reconstruction techniques and assess the optimal compromise of activity recovery and image noise to obtain a reliable 3-dimension map ^{18}F -FDG uptake of the LA wall with sufficient spatial resolution for visualization and analysis of several structure of the LA wall anatomy.
2. To analyze, under metabolic conditions which favor glucose utilization by LA cardiomyocytes, the glucose metabolism through the evaluation of left atrial glucose uptake by ^{18}F -FDG PET/CT in persistent AF and after return to SR.
3. To compare three-dimensional quantitative LA map of low glucose uptake extent with ^{18}F -FDG PET with LGE cMRI, trans-thoracic echography and EAVM for quantify, localizing and evaluating LA fibrosis/structural remodeling/atrial cardiomyopathy and evaluate its value to predict ablation procedural success.

- CHAPTER III - METHOD AND RESULTS -
ARTICLE 1

Article 1:

Prediction of Left Atrial Fibrosis and Success of Catheter Ablation by Speckle Tracking Echocardiography in Patients Imaged in Persistent Atrial Fibrillation

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Background: Non-invasive evaluation of left atrial structural and functional remodeling should be considered in all patients with persistent atrial fibrillation (AF) to optimal management. Speckle tracking echocardiography (STE) has been shown to predict AF recurrence after catheter ablation; however in most studies, patients had paroxysmal AF, and STE was performed while patients were in sinus rhythm.

Aim: The aim of this study was to evaluate the ability of STE parameters acquired during persistent AF to assess atrial fibrosis measured by low voltage area, and to predict maintenance of sinus rhythm of catheter ablation.

Methods: A total of 94 patients (69 men, 65 ± 9 years) with persistent AF prospectively underwent measurement of Global Peak Atrial Longitudinal Strain (GPALS), indexed LA Volume (LAVI), E/e' ratio, and LA stiffness index (the ratio of E/e' to GPALS) by STE prior to catheter ablation, while in AF. Low-voltage area (LVA) was assessed by electro-anatomical mapping and categorized into absent, moderate (>0 to $<15\%$), and high ($\geq 15\%$) atrial extent. AF recurrence was evaluated after 3 months of blanking.

Results: Multivariable regression showed that LAVI, GPALS, and LA stiffness independently predicted LVA extent after correcting for age, glomerular filtration rate, and CHA2DS2-VASc score. Of all the parameters, LA stiffness index had the highest diagnostic accuracy (AUC 0.85), allowing using a cut-off value ≥ 0.7 to predict moderate or high LVA with 88% sensitivity and 47% specificity, respectively. In multivariable Cox analysis, both GPALS and LA stiffness were able to significantly improve the c statistic to predict AF recurrence ($n = 40$ over 9 months FU) over CHARGE-AF ($p < 0.001$ for GPALS and $p = 0.01$ for LA stiffness) or CHA2DS2-VASc score ($p < 0.001$ for GPALS and $p = 0.02$ for LA stiffness). GPALS and LA stiffness also improved the net reclassification index (NRI) over the CHARGE-AF index (NRI 0.67, 95% CI [0.33–1.13] for GPALS and NRI 0.73, 95% CI [0.12–0.91] for LA stiffness, respectively), and over the CHA2DS2-VASc score (NRI 0.43, 95% CI [–0.14 to 0.69] for GPALS and NRI 0.52, 95% CI [0.10–0.84], respectively) for LA stiffness to predict AF recurrence at 9 months.

Conclusion: STE parameters acquired during AF allow prediction of LVA extent and AF recurrence in patients with persistent AF undergoing catheter ablation. Therefore, STE could be a valuable approach to select candidates for catheter ablation.

INTRODUCTION

The management of patients with persistent atrial fibrillation (AF) remains challenging. AF catheter ablation (CA) is recommended for rhythm control to improve symptoms of AF recurrence after failed antiarrhythmic drug therapy and may also be considered as first-line therapy in patients without risk factors for recurrence (1). However, CA is less successful in persistent than in paroxysmal AF (2) and its success is predicted by many factors, among which structural atrial remodeling and atrial scar burden (3) are currently considered the mainstay for AF recurrence (4, 5). Therefore, the decision of whether to pursue CA in persistent AF should be based on considering the risk factors for AF recurrence following the procedure and, in particular, atrial scar burden.

The atrial scar can be assessed by several modalities (6, 7). Cardiovascular magnetic resonance imaging with the late enhancement of gadolinium (LGE-cMR) has been the most studied (8). However, it was found to have no added value to guide ablation strategy (9) and its complexity and limited accessibility restrict its use in clinical practice. LA scar extent may be also evaluated by low-voltage area (LVA) on electroanatomical mapping (EAM) performed during the CA procedure. Several studies showed that extensive LVA extent predicts increased post-ablation arrhythmic recurrences (10, 11). However, because EAM is only available at the time of ablation, this modality is not of value for the selection of CA candidates.

Echocardiography with speckle tracking (STE) allows quantitative assessment of LA volume, LA pressure, LA function, and estimates of LA stiffness could present a non-invasive approach to evaluate atrial structural remodeling. Indeed, LA strain and strain rate were found to correlate with LA fibrosis by LGE-cMR (12) and to be associated with the risk of AF and stroke. STE LA strain was also shown to predict the recurrence of atrial arrhythmias after CA or electrical cardioversion (13–18). However, most studies evaluated STE, while patients were in sinus rhythm (SR) at the time of echocardiographic analysis. Therefore, in this work, we aimed at evaluating the value of STE in homogeneous population of patients being in persistent AF at the time of analysis to assess atrial scar burden by EAM-LVA and to predict the success of CA.

MATERIALS AND METHODS

Study Design and Population

Between January 2018 and April 2021, we prospectively enrolled patients after providing written informed consent to the Institutional Review Board (IRB) approved (2018-17OCT- 389) study protocol (TRIATLON, EudraCT 2019-001813-17A). Inclusion criteria were adult patients with persistent non- valvular AF referred for a first CA procedure according to the ESC guidelines (1) who had preprocedural transthoracic echocardiography (TTE) less than 2 months before undergoing the procedure while being in persistent AF. Patients with a history of congenital heart disease, valvular disease, genetic heart diseases, previous ablation procedure, or those with left atrial appendage thrombus identified at the preoperative transesophageal echocardiography contraindicating CA were not considered for inclusion.

Clinical Parameters

All patients underwent clinical examination, ECG, and comprehensive laboratory testing, including full blood count, and evaluation of renal, hepatic, and thyroid function prior to CA. We prospectively recorded coefficient of variation (CV) risk factors, duration of AF, known obstructive sleep apnea, and computed CHA₂ DS₂ -VASc, HATCH, and APPLE risk scores for recurrence of AF as well as HAS-BLED score for risk of bleeding. Symptom severity was classified with EHRA score.

Echocardiography

Pre-intervention two-dimensional (2D) TTE was acquired while patients were in AF using IE33 or EPIC echocardiographic systems (Philips Healthcare, Andover, MA, United States) and stored digitally on a PACS system (Philips Intellispace). Images were analyzed offline by one observer (SMA) and all measurements were performed by averaging 2 cardiac cycles. Left ventricular (LV) volumes and ejection fraction were calculated using Simpson's biplane method. The E/e' ratio was calculated by the dividing peak mitral flow E wave by the average of septal and lateral e' tissue Doppler velocities.

LA volume and strain analysis were performed on dedicated apical 4 and 2-chamber views of the LA acquired with a frame rate between 60 and 80 frames per second and analyzed using Image-ArenaTM cv4.6 (TomTec Imaging Systems, Unterschleissheim, Germany) in duplicate by two experienced blinded echocardiographers (SMA and QG). The LA endocardium was traced automatically with manual adjustment if needed. According to the recommendation of the EACVI/ASE Task Force, Reservoir Global Peak Atrial Longitudinal Strain (GPALS) was

computed using LV end-diastole as zero-strain point. Maximal and minimal LA volume was measured, respectively, at the end of LV systole and at the end of the LV diastole and indexed to the body surface area (LAVI). LA fractional area change (FAC) and ejection fraction (LAEF) of passive emptying fraction were computed, respectively, as the percentage ratio of change of LA area and volume during systole. LA stiffness index (LASI) was calculated as E/e' divided by GPALS (19).

Electroanatomical Mapping and Catheter Ablation

Electrical cardioversion was attempted at the beginning of the procedure prior to ablation. EAM of the LA was obtained using the ConfiDENSE™ CARTO3 system v6.0.70 using the 2515 Variable Loop Lasso Multi-Electrode Eco Nav (Biosense Webster, Diamond Bar, CA, United States) using at least 1,000 measurements. LVA was defined as bipolar peak-to-peak voltage amplitude of <0.5 mV in SR and <0.31 mV in AF. The total LVA extent was calculated as the percentage of LA surface and patients were separated into 3 groups of LVA extent: Group I (absent): LVA = 0%, Group II (moderate): LVA >0 and $\leq 15\%$, and Group III (high): LVA $>15\%$ (Figure 1). All patients underwent radiofrequency PVI. Additional lines or complex atrial fractionated electrogram (CAFE) ablations were performed at the physician's discretion.

Clinical Follow-up

Patients underwent clinical follow-up and ECG at 3 months, 6 months, and 1 year as well as 24-h ambulatory Holter monitoring at 6 months after CA. Additionally, surface ECG, ambulatory ECG, and/or cardiac event recording values were obtained when patients presented symptoms of arrhythmia recurrence. Any detectable atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) of at least 30 s beyond a 3-month blanking period after the procedure was considered as recurrence.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, United States) and R 3.5. Continuous values were tested for normality by Q-Q plots, histograms, and the Kolmogorov–Smirnov test. Normally and non-normally distributed baseline parameters between different LVA stages were expressed as the mean $\pm$ SD and median and interquartile range (IQR) and were compared, respectively, using one-way ANOVA or Kruskal–Wallis test when not normally distributed. Post hoc comparison between groups was performed using Tukey's test and the Wilcoxon rank-sum test, as appropriate. Categorical data were compared

using the Chi-square test. A p-value < 0.05 was considered indicative of a statistically significant difference. The relationship between LVA and echocardiographic parameters was evaluated by linear regression analysis and the Pearson correlation coefficient. Uni- and multivariable binary logistic regression analyses were used to determine associative factors predicting moderate (Group II) or important (Group III) LVA extent, respectively. Parameters with significant collinearity were not allowed to simultaneously enter the multivariable model. Collinearity was evaluated by multiple regression analysis between parameters and we considered evident collinearity when tolerance (1-R²) was <0.2 or variance inflation factor >5. Receiver operating characteristic (ROC) analysis was performed using the roc.test function in the pROC package, and areas under ROC curves were compared pairwise using the Delong test. Optimal sensitivity and specificity were determined by the highest Youden index. Recurrence-free survival was related to the individual clinical parameters, LVA extent, and echocardiographic covariables, and was evaluated using Kaplan–Meier survival graphs and uni- and multivariable Cox proportional hazard regression models. We also evaluated the incremental benefit of GPALS and LA stiffness, to improve the prediction of AF recurrence over either CHARGE-AF or CHA2 DS2 -VASc score by computing the increase in the c statistic in the Cox model and by computing their net reclassification index (NRI).

Intraobserver and interobserver reproducibility of strain measurements were assessed in 10 randomly selected patients and expressed as CV and intraclass correlation coefficient (ICC) with 95% confidence interval. The CV was expressed as a percentage (mean/SD).

RESULTS

Patient Characteristics

Patient baseline characteristics are summarized in Table 1. A total of 94 patients (69 men, mean age 65 ± 9 years) were included. AF persisted for <1 year in 86 (91%) patients and for >1 year in 8 (9%) patients. Also, 72% of patients were under antiarrhythmic medications. Mean CHA2DS2-VASc score was 2.3 ± 1.6 and 11 (12%) patients had a history of stroke/TIA or systemic thromboembolism. Notably, 51 patients (54%) were hypertensive, 13 (14%) had coronary artery disease, 11 (12%) had diabetes mellitus, and 15 (16%) had sleep apnea.

Electroanatomical mapping was successfully performed in 74 patients (79%) during AF and in 20 patients (21%) during SR (after cardioversion during CA procedure). LVA was observed in 56 (60%) patients with a median extent of 2.5% (range 0–64%). By EAM, 38 patients had no

LVA (Group I), 37 patients had moderate LVA (Group II), and 19 patients had important LVA extent (Group III). The patients in the higher LVA groups were older, had lower estimated glomerular filtration rate (eGFR), and higher CHA2 DS2 -VASc, CHARGE-AF, and HAS-BLED scores. However, there was no difference in the coronary artery risk factors, AF duration, EHRA scores, or in antiarrhythmic drug therapy between the different groups.

Catheter Ablation

The procedural characteristics are summarized in Table 2. PVI was successfully performed in all patients. Box isolation, other lines, and CAFE were performed more frequently in patients with higher LVA. There were no complications of cardiac perforation, systemic embolism or stroke, atrial-esophageal fistula, pulmonary stenosis, or death.

Echocardiographic Parameters and Relation to Low-Voltage Area Extent

Table 1 summarizes the baseline 2D echocardiographic and STE findings. The patients in the moderate or high LVA extent groups had a significantly larger indexed LA volume (Figure 2A), higher E, and lower e' wave velocities and thus higher E/e' ratio (Figure 2B), lower LA ejection fraction, FAC and GPALS (Figure 2C), and greater LA stiffness (Figure 2D). However, there was no difference in the LV ejection fraction or LV mass index between the three groups of patients. LVA extent correlated significantly but poorly with LAVI ($r = 0.20$, $p > 0.001$) and better with GPALS ($r = 0.38$, $p > 0.001$), E/e' ratio ($r = 0.39$, $p > 0.001$), and especially with LA stiffness ($r = 0.49$, $p > 0.001$). By logistic regression analysis, the presence of LVA was significantly associated with age, eGFR, diuretics use, and with CHA2 DS2 -VASc, HAS-BLED, and CHARGE-AF risk scores (Table 3). Because of the association between GPALS, E/e' ratio and LA stiffness, multivariable analysis was presented as two models, including either E/e' and GPALS or LA stiffness. Multivariable analysis demonstrated that LAVI, and either GPALS or LA stiffness remained independently associated with presence of LVA after correcting for clinical parameters, such as age, eGFR, and CHA2 DS2 -VASc score (Table 3).

The ROC analysis for prediction of any ($>0\%$) and important ($>15\%$, Group III) LVA extent is shown in Figures 3A,B, respectively. LA stiffness had the highest AUC (0.78), for prediction of overall LVA extent, which was significantly ($p < 0.05$) greater than that of E/e' ratio. Also, for prediction of important LVA extent, LA stiffness had the highest AUC (0.85), which was significantly higher than that of LAVI (AUC 0.64, $p = 0.03$) and GPALS (AUC 0.75, $p = 0.01$). A cut-off value of GPALS $\leq 10\%$ allowed to predict moderate or important LVA with a sensitivity

of 86 and 53% specificity, respectively, while LA stiffness ≥ 0.7 had 88% sensitivity and 47% specificity to predict important LVA.

Prediction of Catheter Ablation Success Rate

After CA procedure, 60 patients (67%) were discharged with beta-blockers, 10 patients (11%) with sotalol, 24 patients (26%) with amiodarone, and 20 patients (21%) with class I AAR drugs. During a median of 9 [6; 11] months of follow-up, 40 (43%) patients had arrhythmia recurrence. Patients with recurrent atrial tachyarrhythmias were older (68 ± 6 vs. 64 ± 10 years, $p = 0.009$), more often hypertensive (68% vs. 43%, $p = 0.02$), and had a higher HAS-BLED score. By contrast, there were no differences in the CHA₂DS₂-VASc (2.6 ± 1.3 vs. 2.1 ± 1.8 , $p = 0.11$), HATCH (1.7 ± 1.1 vs. 0.35 ± 1.34 , $p = 0.47$), and APPLE risk scores (2.6 ± 0.9 vs. 2.5 ± 1.1 , $p = 0.68$), or according to antiarrhythmic drug treatment administered after CA procedure [20 patients (49%) vs. 27 patients (51%), $p = 0.55$] between patients with and without AF recurrence. Patients with AF recurrence had however significantly lower GPALS ($7.6 \pm 3.8\%$ vs. $9.9 \pm 4.6\%$, $p = 0.007$) and greater LA stiffness (1.7 ± 1.3 vs. 1.1 ± 0.9 , $p = 0.04$). Although LVA extent was greater in patients with recurrent atrial tachyarrhythmias (median 6.3; IQR 14.6) than in those with successful CA (median 0.7; IQR 8.7, $p = 0.05$), there were no significant differences ($p = 0.35$) of AF recurrence between patients with no (34%), moderate (46%), and high (53%) LVA.

Uni- and multivariable Cox regression analysis of AF recurrence is summarized in Table 4. Univariable predictors of AF recurrence were age, body mass index (BMI), hypertension, HAS-BLED score, GPALS, and LA stiffness as well as the presence of any LVA. Low GPALS and elevated LASI remained strong independent predictors of recurrent atrial tachyarrhythmias following CA procedures (Table 4) in multivariable analysis after correcting for the other clinical parameters.

The ROC curves for prediction of AF recurrence after the CA procedure for the different echocardiographic parameters are shown in Figure 4 and Kaplan–Meier curves are shown in Figure 5. LA stiffness had the highest AUC (0.685) to predict AF recurrence, which was significantly higher ($p = 0.02$) than that of the Apple score (AUC 0.54) and LAVI (AUC 0.561, $p = 0.05$ vs. GPALS). Both GPALS and LA stiffness had similar ($p = 0.23$ and 0.07 , respectively) good predictive accuracy to predict AF recurrence than LVA. Both GPALS and LA stiffness were able to significantly improve the c statistic to predict AF recurrence over CHARGE-AF (c score = 0.465, c score of GPALS + CHARGE-AF = 0.713, $p < 0.001$, c score of LA stiffness and CHARGE-

AF = 0.686, $p = 0.01$), or CHA2DS2-VASc score (c score = 0.579, c score of GPALS and CHA2DS2-VASc = 0.687, $p < 0.001$, c score of LA stiffness and CHA2DS2-VASc = 0.685, $p = 0.02$). GPALS and LA stiffness also improved the NRI over the CHARGE-AF index (NRI 0.67, 95% CI [0.33–1.13] for GPALS and NRI 0.73, 95% CI [0.12–0.91] for LA stiffness, respectively), and over the CHA2 DS2 -VASc score (NRI 0.43, 95% CI [–0.14 to 0.69] for GPALS and NRI 0.52, 95% CI [0.10–0.84], respectively) for LA stiffness to predict AF recurrence at 9 months.

Intraobserver and Interobserver Variability

Interobserver CV values were $10.2 \pm 13.8\%$ for LAVI, $-0.5 \pm 2.5\%$ for GPALS, $4 \pm 6\%$ for E/e' ratio, and $0.2 \pm 0.2\%$ for LA stiffness, respectively. Interobserver ICC were 0.98 [0.93; 0.99] for LAVI, 0.86 [0.45; 0.97] for GPALS, 0.95 [0.89; 0.98] for E/e' ratio, and 0.98 [0.98; 0.99] for LA stiffness, respectively (all $p < 0.001$).

Intraobserver CV values were $3.2 \pm 10.8\%$ for LAVI, $0.4 \pm 0.9\%$ for GPALS, $3 \pm 5\%$ for E/e', and 0.1 ± 0.3 for LA stiffness, respectively, and the corresponding ICC were 0.98 [0.93; 0.99], 0.96 [0.86; 0.99], 0.97 [0.93; 0.99], and 0.98 [0.94; 0.99], respectively (all $p < 0.001$).

	All n=94	LVA Group I (0% LVA) n=38	LVA Group II (LVA 0-15%) n=37	LVA Group III (LVA >15%) n=19	P value
Clinical Characteristics					
Age (years)	65±9	62±9	66±8	69±5	0.008
Sex (male)	69(73%)	30(79%)	29(78%)	10(53%)	0.07
BMI (kg/m2)	29±5	29±5	29±5	28±5	0.62
Hypertension	50(53%)	17(45%)	20(54%)	13(68%)	0.24
Hypercholesterolemia	46(49%)	20(53%)	15(41%)	11(56%)	0.40
Diabètes	11(12%)	5(13%)	4(11%)	2(10%)	0.94
Family history of CAD	27(29%)	14(37%)	13(35%)	7(37%)	0.16
Smoking	29(30%)	14(37%)	13(35%)	1(5%)	0.03
CAD	13(14%)	5(13%)	5(13%)	3(16%)	0.49
Chronic lung disease	19(20%)	10(26%)	5(13%)	4(21%)	0.39
Sleep Apnea	15(16%)	6(16%)	7(19%)	2(11%)	0.42
Systolic blood pressure (mmHg)	129±16	131±15	128±17	128±19	0.63
Diastolic blood pressure (mmHg)	79±12	79±13	77±11	81±10	0.54
Heart rate (bpm)	83±20	81±21	86±20	82±17	0.82
eGFR (ml/min)	76±17	82±15	75±17	66±18	0.005
Stroke/TIA history	11(12%)	6(16%)	5(14%)	3(16%)	0.63
Vascular disease	15(16%)	8(21%)	4(11%)	3(16%)	0.49
AF duration > 6 months	35(37%)	11(29%)	13(35%)	11(58%)	0.12
CHA ₂ DS ₂ -VASc Score	2.3±1.6	1.9±1.3	2.3±1.7	3.2±1.4	0.011
CHARGE-AF Score	12.7±1.0	12.4±1.1	12.8±0.9	13.0±1.0	0.063
HATCH Score	1.7±1.3	1.4±1.2	1.7±1.3	2.5±1.2	0.002
APPLE Score	2.6±1.0	2.2±1.1	2.6±0.9	3.2±1.0	0.006
HAS-BLED Score	1.4±1.1	1.1±1.0	1.4±1.1	2.1±0.8	0.004
EHRA Score	I 15(16%) II 47(50%) III 30(32%) IV 2(2%)	8(21%) 16(42%) 13(34%) 1(3%)	6(16%) 20(54%) 11(30%) 0(0%)	1(5%) 11(58%) 6(32%) 1(5%)	0.59
Medications before CA					
β-blockers	66(70%)	24(63%)	27(73%)	15(79%)	0.43
Sotalol	8(9%)	5(13%)	3(8%)	0(0%)	0.25
Amiodarone	20(21%)	6(16%)	10(27%)	4(21%)	0.50
AAR class I	18(19%)	9(21%)	6(16%)	4(21%)	0.77
Digoxin	4(4%)	2(5%)	2(5%)	0(0%)	0.60
Echocardiography					
LVEF(%)	56±39	56±16	55±12	57±14	0.88
LV mass index (g/m2)	93±28	86±22	100±30	101±29	0.08
LA diameter (mm)	44±6	42±6	46±5	46±5	0.02
LAVI (ml/m2)	59±19	50±13	63±19	64±19	<0.001
E wave (cm/s)	80±20	76±16	80±20	89±22	0.07
Average e' (cm/s)	9.5±2.6	10.8±2.5	9.0±2.6	8.1±1.4	0.002
E/e'	9.1±3.2	7.9±2.5	9.0±3.3	11.4±2.9	<0.001
LAEF (%)	19±11	22±14	18±6	15±9	<0.001
LA-FAC (%)	14±7	16±8	13±4	11±6	0.02
GPLAS (%)	8.9±4.5	11.3±5.3	7.9±2.6	6.2±2.9	<0.001
LA Stiffness	1.4±1.1	0.8±0.4	1.3±0.8	2.5±1.6	<0.001

TABLE 1 | Study population: AF, atrial fibrillation; AAD, anti-arrhythmic drugs; BMI, body mass index; EDV, left ventricular end diastolic volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESV, end systolic volume; FAC, left atrial fractional area change; GPALS, Global Peak Atrial Longitudinal Strain; LA, left atrium; LAVI, left atrial volume indexed; LV, left ventricular; TIA, transient ischemic attack. II Post hoc comparison $p < 0.05$ vs. Group II. III Post hoc comparison $p < 0.05$ vs. Group III.

		LVA Group I	LVA Group II	LVA Group III	
	All	(0% LVA)	(LVA 0-15%)	(LVA >15%)	P value
	n=94	n=38	n=37	n=19	
LVA extent	8±12	0±0	6±4	27±15	p<0.001
AF rhythm during EAM	74(79%)	28(73%)	30(81%)	16(84%)	0.11
PVI	94(100%)	38(100%)	37(100%)	19(100%)	NA
CTI	22(23%)	12(32%)	8(22%)	2(10%)	0.20
Posterior Wall isolation	26(28%)	1(3%)	12(32%)	13(68%)	<0.001
Mitral Isthmus	17(18%)	1(3%)	7(19%)	9(47%)	<0.001
CAFE	6(6%)	0(0%)	2(5%)	4(21%)	0.01
Procedural time(min)	173±42	162±42	176±39	188±43	0.08

TABLE 2 | Procedural characteristics: AF, atrial fibrillation; CAFE, complex atrial fractionated electrogram; CTI, cavo-tricuspid isthmus ablation; EAM, electroanatomical mapping; LVA, low-voltage area; NA, not applicable; PVI, pulmonary vein isolation; TS, trans-septal puncture. II Post hoc comparison $p < 0.05$ vs. Group II. III Post hoc comparison $p < 0.05$ vs. Group III.

	Univariable analysis		Multivariable Model 1		Multivariable Model 2	
	OR [95%CI]	P value	HR [95%CI]	P value	OR 95% CI	P value
Age	1.08 [1.02;1.14]	0.007	0.99 [0.89;1.09]	0.848	1.00 [0.91;1.10]	0.945
Sex	1.07 [1.02;1.13]	0.32				
BMI	1.63 [0.62;4.29]	0.65				
Diabetes	0.97 [0.89;1.07]	0.72				
Hypertension	1.26 [0.35;4.47]	0.18				
Charge-AF risk score	0.56 [0.24;1.29]	0.03				
CAD	0.48 [0.18;1.24]	0.85				
Pulmonary disease	0.89 [0.26;2.96]	0.23				
eGFR	1.86 [0.67;5.14]	0.009	0.96 [0.92;1.00]	0.06	0.96 [0.93;1.00]	0.078
ARB/ACEI	0.96 [0.93;0.99]	0.06				
Loop diuretics	0.36 [0.13;1.02]	0.03				
AAR	0.29 [0.09;0.87]	0.09				
CHA2DS2-VASC score	0.16 [0.01;1.35]	0.03	1.11 [0.68;1.79]	0.671	1.07 [0.66;1.75]	0.763
HAS-BLED Score	1.36 [1.02;1.81]	0.02				
AF duration	1.62 [1.06;2.47]	0.87				
Total # of episodes of AF	0.86 [0.67;1.17]	0.29				
LVEF(%)	0.99 [0.96;1.03]	0.90				
LV mass index	1.01 [0.99;1.04]	0.11				
LAVI	1.05 [1.02;1.09]	0.001	1.06 [1.01;1.11]	0.016	1.06 [1.01;1.11]	0.011
E wave	1.02 [0.99;1.04]	0.09				
e' wave	0.66 [0.50;0.88]	0.005				
E/e'	1.30 [1.06;1.59]	0.009	1.21 [0.95;1.55]	0.115		
LA EF	0.95 [0.91;0.99]	0.037				
FAC	0.91 [0.84;0.98]	0.012				
GPALS	0.73 [0.62;0.86]	< 0.001	0.78 [0.64;0.96]	0.02		
LA Stiffness	8.24 [2.52;26.9]	< 0.001			4.97 [1.34;18.4]	0.016

Table 3: Uni and Multivariable logistic regression analysis for Predictors of LVA: Abbreviations: OR: Odds ratio, all others as table 1.

	Univariable analysis		Multivariable Model 1		Multivariable Model 2	
	HR [95%CI]	P value	HR [95%CI]	P value	HR [95%CI]	P value
Age	1.03 [0.99;1.07]	0.103	0.97 [0.92;1.02]	0.237	1.00 [0.95;1.05]	0.896
Sex	0.59 [0.30;1.16]	0.130				
BMI	0.93 [0.86;1.00]	0.050	0.91 [0.85;0.99]	0.026	0.90 [0.83;0.98]	0.026
Diabetes	0.94 [0.36;2.40]	0.897				
Hypertension	1.92 [0.99;3.72]	0.054	1.50 [0.58;3.87]	0.402	1.31 [0.48;3.54]	0.594
Charge-AF risk score	1.11 [0.82;1.49]	0.483				
CAD	1.13 [0.51;2.48]	0.761				
Pulmonary disease	0.80 [0.35;1.81]	0.597				
eGFR	0.98 [0.96;1.00]	0.185				
Loop diuretics	1.87 [0.96;3.66]	0.065				
CHA2DS2-VASC score	1.10 [0.90;1.33]	0.326				
HATCH score	1.03 [0.77;1.37]	0.841				
APPLE score	1.09 [0.85;1.39]	0.468				
HAS-BLED Score	1.37 [1.03;1.82]	0.031	1.13 [0.70;1.82]	0.609	1.12 [0.70;1.80]	0.616
Total # of episodes of AF	0.98 [0.80;1.20]	0.883				
Any LVA	1.95 [1.0 ;3.78]	0.04				
LVEF(%)	1.00 [0.97;1.02]	0.995				
LV mass index	0.99 [0.97;1.00]	0.192				
LAVI	1.00 [0.99;1.02]	0.297				
E wave	4.21 [0.69;25.6]	0.118				
E/e'	1.05 [0.95;1.15]	0.334				
LA EF	0.98 [0.95;1.00]	0.155				
FAC	0.95 [0.91;1.00]	0.067				
GPALS	0.89 [0.78;0.95]	0.003	0.85 [0.77;0.95]	0.004		
LA Stiffness	1.34 [1.08;1.65]	0.006			1.30 [1.03;1.65]	0.026

Table 4: Uni and Multi variable Cox analysis for predictors of AF recurrence after CA: Abbreviations: HR, hazard ratio; all others as table 1.

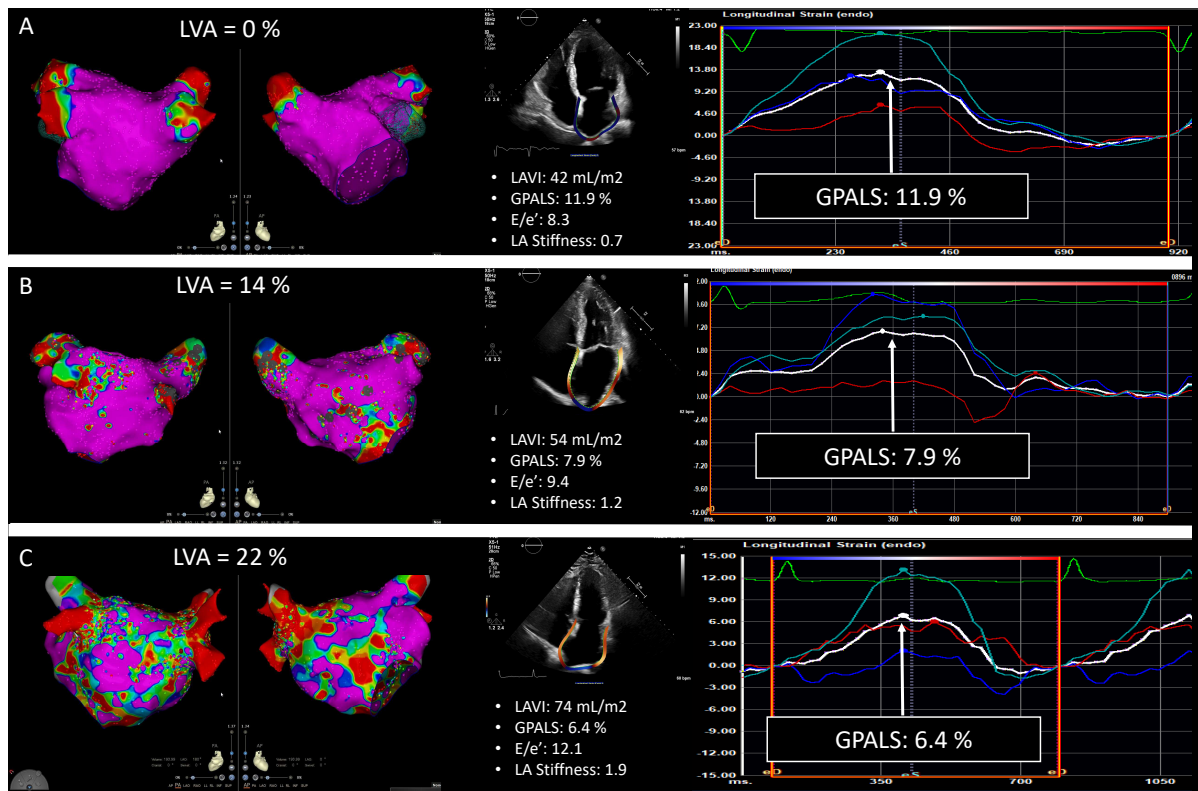


Figure 1: Representative example of echocardiographic strain analysis performed in three patients with different severity of left atrial (LA) Low Voltage Area (LVA) extent. Group I: no LVA (top panels), group II: moderate LVA extent (middle panels) and group III: important LVA extent (bottom panels). The color gradient of the LVA maps indicates electrogram amplitude from pink (>0.5 mV in SR and >0.31 in AF) to red at <0.1 mV.

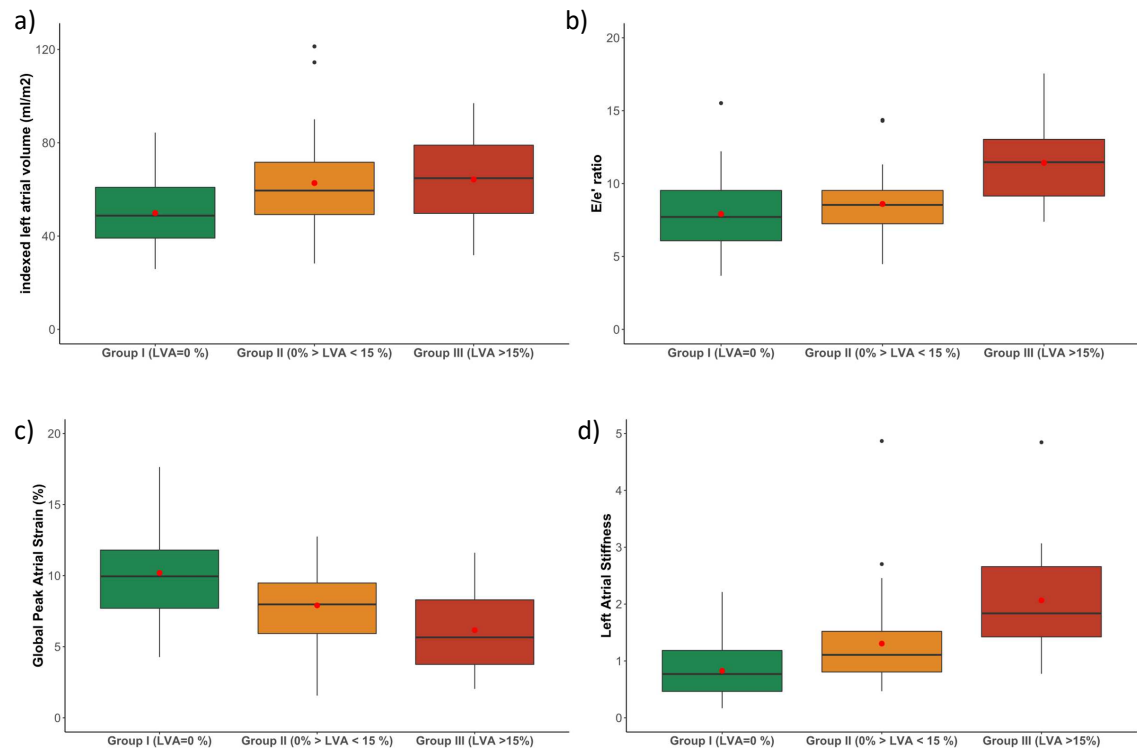


Figure 2: Indexed left atrial volume (panel a), E/e' ratio (panel b), Global Peak Atrial Longitudinal Strain (GPALS)(panel c) and Left Atrial Stiffness (panel d) in patients with permanent AF according to their stages of Low Voltage Area extent. The box represents interquartile range, the line indicates the median value, whiskers show minimum/maximum values, mean value is shown as a red dot and outliers as black dots.

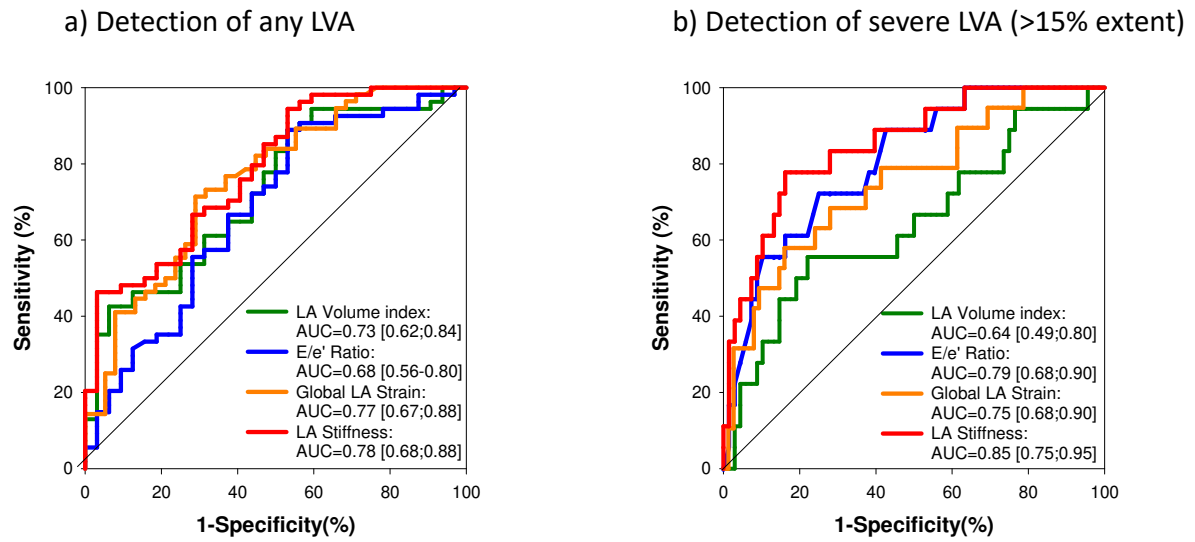


Figure 3a Receiver-operating characteristic curve analysis for prediction presence of any LVA during EAM (Group II and III). AUC, Area Under the Curve; $p < 0.05$ Global LA strain vs E/e' ratio.

Figure 3b Receiver-operating characteristic curve analysis for prediction presence of important LVA extent (Group III LVA >15%) during electroanatomical mapping (EAM). AUC, Area Under the Curve; $p < 0.05$ LA strain vs LAVI.

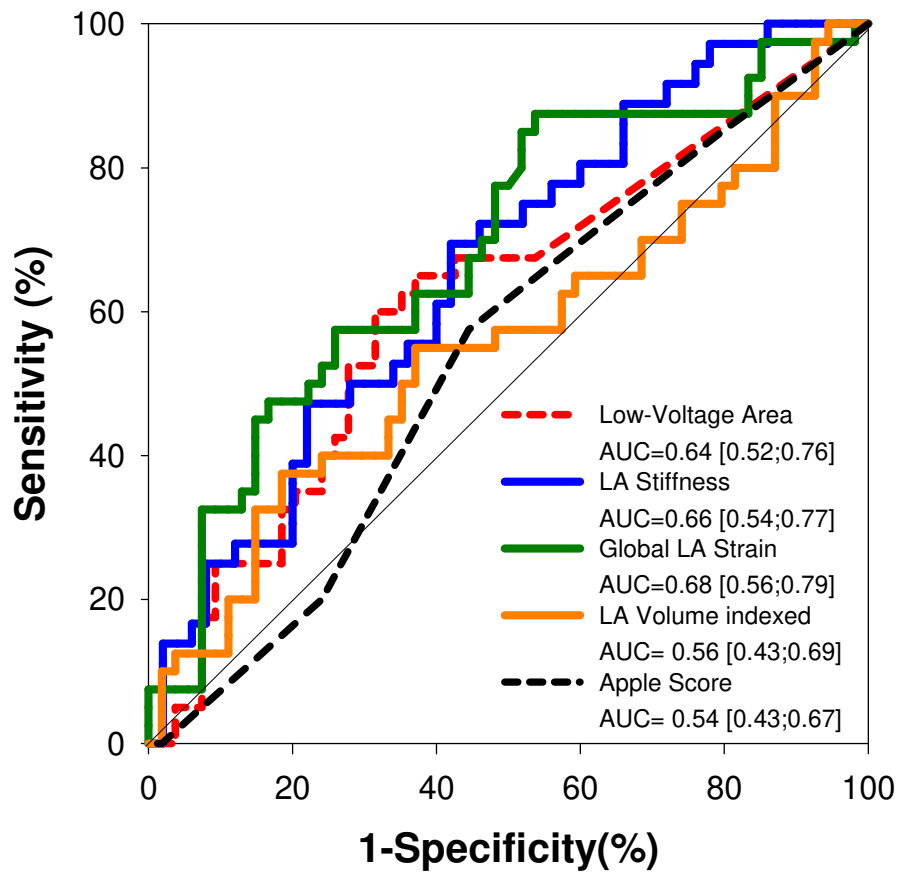


Figure 4: Receiver-operating characteristic curve analysis for prediction atrial fibrillation recurrence after catheter ablation AUC, Area Under the Curve; $p=0.02$ GPLAS vs Apple Score and $p=0.05$ GPLAS vs LAVI.

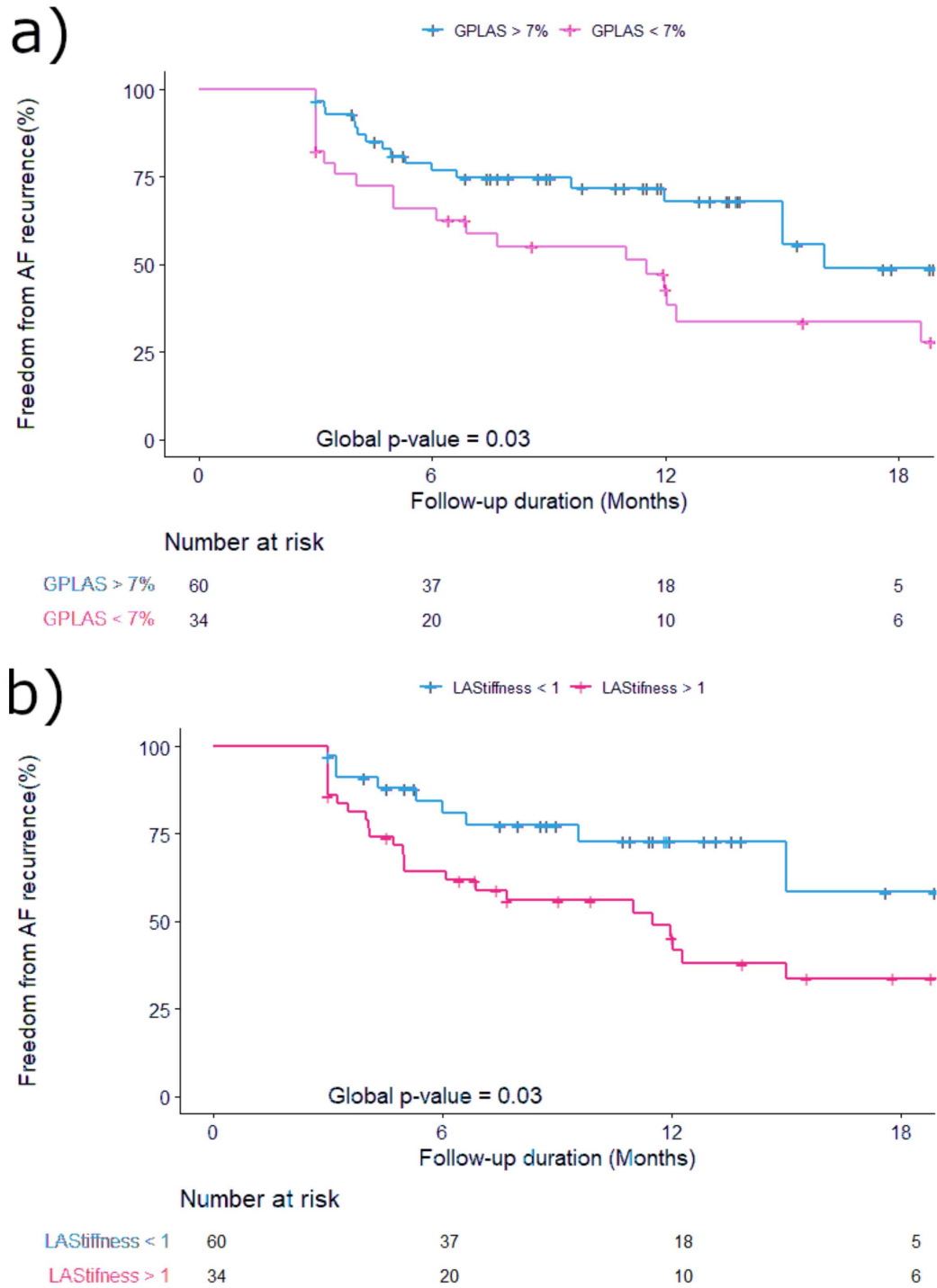


Figure 5: Kaplan Meyer Graphs showing freedom from AF recurrence after CA according to GPLAS (a) and LA strain (b)

DISCUSSION

We performed a non-invasive evaluation of LA structure and function acquired in patients while being in persistent AF before CA. The salient findings of our study were as follows:

1) LAVI, E/e' GPALS, and LA stiffness during persistent AF independently allowed to predict LVA during electro-anatomical mapping. Of all the parameters, LA stiffness had the highest diagnostic accuracy for the prediction of LVA.

2) GPALS and LA stiffness are also able to predict the success of CA procedures and maintenance of SR with similar accuracy as LVA extent. For this purpose, the predictive accuracy of GPALS is significantly better than the APPLE score and LAVI.

3) These new echocardiographic parameters evaluated in AF had high reproducibility and a low intraobserver and interobserver variability.

To the best of our knowledge, this is the first study comparing the predictive value of strain with LVA in a homogeneous population of patients being in persistent AF at the time of analysis. Structural and functional atrial remodeling is a well-established hallmark involved in the development and progression of AF (3). It is strongly associated with the development of progressive atrial fibrosis, which will ultimately lead to AF persistence. In the present work, we compared different non-invasive structural and functional parameters of LA remodeling to EAM-derived LVA extent as the reference method for evaluation of atrial fibrosis. EAM evaluates atrial voltage with predefined thresholds to identify LVA associated with the atrial scar. This widely used electrophysiological technique for atrial scar quantification has been validated against histopathology (20) and was found to have comparable results to the LGE-cMR based atrial scar quantification both in SR (21–23) and in AF (24, 25). LA dilatation is a well-known parameter associated with atrial remodeling severity before and during AF and was shown to be associated with poorer ablation outcomes and higher recurrence rates (26). Our study confirmed these findings to be associated with LVA. Moreover, the E/e' ratio, a parameter indicative of increased LV filling, and hence of increased LA pressures, was associated with larger regions of LVA. This causal relationship is probably explained by the increased LA pressure and wall stress leading to structural remodeling and reduced atrial

pump function (27). Similar findings of E/e' ratio correlating with atrial fibrosis have been already illustrated, however, only in SR (16, 28). Our results corroborated that the association between LA pressure estimated by E/e' and LA remodeling evaluated by LVA extent also remains valid in the setting of AF. In our study, the prediction of LVA was even more accurate for GPALS and LA stiffness. In SR, LA strain has three components: the reservoir function, the conduit function, and the contractile function (booster pump). Several studies have shown that the atrial booster pump and reservoir function has an important prognostic role in the prediction of AF occurrence (12, 29). In patients in SR, a relationship between the extent of LVA and LA strain and LA emptying fraction was reported (30). In AF, however, booster pump strain is absent, and only GPALS, a surrogate of LA conduit/reservoir function, can be assessed. GPALS by STE in SR was shown to inversely correlate with atrial fibrosis by histopathology in patients with mitral valve regurgitation undergoing valve surgery (31) and also in patients with advanced heart failure undergoing heart transplantation (32). To our knowledge, only a few studies evaluated the relation of LA strain to predict fibrosis during AF. Kuppahally et al. (12) found LA strain and strain rate to be inversely related to LA wall fibrosis, by LGE-cMR in patients with paroxysmal or persistent AF, but in this cohort, a minority (29%) of patients were studied while in AF. LA stiffness is another parameter of interest but has been less evaluated. It is computed as the ratio of E/e' to LA peak strain (19). It thus represents an estimate of LA compliance estimated from two non-invasive measurements of LA deformation (strain) and atrial pressure (estimated from E/e' ratio). Indeed, E/e' —the ratio of the early diastolic velocity of the mitral inflow to early diastolic velocity of the mitral annulus provides a close approximation of LV filling pressures in a wide spectrum of diseases. At the time of mitral valve opening, peak LA pressure is equal to LV filling pressure, and thus, E/e' can be considered as a substitute for LA peak pressure. Kishima et al. (17) demonstrated a relation between LA stiffness and LVA, however, only in patients with paroxysmal AF who underwent STE while in SR. In this context, the principal novelty of our study is the demonstration of the usefulness of the different parameters to predict atrial fibrosis by LVA while being in AF.

Another important finding of our study was the demonstration that GPALS and atrial stiffness can predict the success of CA. It has been well demonstrated that atrial fibrosis estimated by LGE-cMR (33) or LVA (10, 11) predicts an increased risk of post-ablation arrhythmia recurrence. In our present study, clinical risk scores, such as the CHARGE- AF CHA2DS2-VASc, HATCH, or APPLE, were predictive of arrhythmia recurrence, and the only clinical score

associated with arrhythmia recurrence was the HAS-BLED score. As expected, advanced age, increased BMI, history of systolic arterial hypertension, and the degree of atrial fibrosis estimated by LVA predicted the risk of AF recurrence. However, the estimation of atrial function by GPALS and LA stiffness had a similar good predictive value as LVA. While other studies had already linked parameters, such as LAVI, E/e' GPALS, and atrial stiffness with AF recurrence, this was mostly shown in patients with paroxysmal AF during SR (14–18).

Clinical Implications

The success rate of CA in persistent AF is lower than in paroxysmal AF and is determined by the duration of AF and the degree of LA structural remodeling. Therefore, for the decision of AF CA, it is recommended to consider the risk of AF recurrence (1). Whereas EAM-LVA is a straightforward procedure for the electrophysiologist, providing rapid information on structural remodeling, this test has little usefulness for the selection of patients, as it is invasive and can only be performed when the decision of CA has already been taken. LGE-cMR is currently the only well-validated non-invasive technique to evaluate LA fibrosis; however, it is time-consuming, has limited accessibility, and the reproducibility of exact quantification of the degree of fibrosis is not standardized. This restricts its clinical use to expert centers. Echocardiography is more readily available and less expensive. We showed that the GPALS and atrial stiffness measurements have high interobserver and intraobserver reproducibility and that their predictive value for AF recurrence was non-inferior to LVA. This suggests that this simple test could be useful for the preoperative selection of candidates for CA.

Limitations

This was a single-center study with limited clinical follow-up. Our LVA measurements might not be applicable to other mapping systems and catheters. While all echocardiography exams were performed in AF, EAM was performed both in AF and in SR. It was however demonstrated that LVA measurements between AF and SR correlate well when a lower voltage cutoff is used in AF (34, 35), as we did in our present study. Echocardiographic acquisitions were performed from an average of only two cardiac cycles. Averaging more cycles might have lowered the beat-to-beat variability of measurements in AF. TTE was analyzed in duplicate by two experienced blinded echocardiographers (SMA and QG). The researchers were not independent. These results should be confirmed using other vendors because of the inter-vendor variability. We did not use long-term ECG monitoring, and therefore, we might have not been able to detect all asymptomatic episodes of AF during

follow-up. Our findings should therefore also be confirmed with long-term arrhythmia monitoring. Finally, we did not perform LGE-cMR, and therefore, we could not evaluate whether STE measurements would have had better predictive accuracy to predict CA success than this technique.

CONCLUSION

In subjects with persistent AF, there is a significant correlation between indexed LA volume, GPALS, the LA pressure estimated by E/e' ratio, and LA stiffness – acquired during AF – and the degree of LVA. In addition, low GPALS and elevated LA stiffness predicted a higher recurrence rate of atrial tachyarrhythmias after the index CA procedures. This supports the use of STE to non-invasively predict the severity of atrial fibrosis and the success of CA procedures in patients with persistent AF.

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- CHAPTER III - METHOD AND RESULTS -
ARTICLE 2

Article 2:

Cardiac atrial metabolism quantitative assessment with analog and digital TOF- PET/CT

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Abstract

Background: Evaluation of left atrial (LA) remodeling is becoming increasingly relevant in understanding several pathological cardiac conditions. 18F-FDG-PET/CT, the current gold standard for metabolic evaluation of the left ventricle, could be extended to LA using the latest PET technologies. We sought to perform a phantom study to optimize the reconstruction algorithm in this context.

Methods: The liver, heart cavity and walls of an anthropomorphic phantom were filled with typical patient 18F-FDG activity concentrations. Acquisitions were performed on an analog and on a digital TOF-PET/CT, and reconstructed with and without resolution recovery (RR). The Richardson-Lucy RR method was used, either through a third-party software, or through the PET/CT manufacturer algorithm. Activity recoveries in the atria and ventricles and signal-to-noise ratios were evaluated to identify the best reconstruction and RR parameters. The same methodology was applied on a patient cardiac study.

Results: Analog PET/CT with the third-party RR cannot improve the activity recovery without markedly degrading the image quality. For the digital PET/CT, the optimal algorithm was the manufacturer RR reconstruction using 4 iterations and 15 subsets combined with 5 RR iterations. This reconstruction improved the LA activity recovery from 58% to 70% while preserving images of diagnostic quality. Similar results were obtained for the patient study.

Conclusions: The digital TOF-PET/CT with the identified optimal reconstruction can be used to quantitatively analyze the LA uptake in 18F-FDG cardiac studies while still preserving image reading quality. This may lead to more precise cardiovascular disease status evaluation, especially when atria are concerned.

Background

The prognostic value of the left atrium (LA) remodeling as biomarker of outcome in several cardiovascular diseases, such as atrial fibrillation or heart failure with preserved ejection fraction, is becoming increasingly recognised [1]. Echocardiography, cardiac magnetic resonance or cardiac computed tomography have emerged as interesting non-invasive imaging techniques able to evaluate left atrial remodeling in response to electrical, mechanical or metabolic stressors [2,3]. On the other hand, LA remodeling can also be characterized from his metabolic changes observed by ^{18}F - FDG imaging with PET/CT [4-6]. In fact, this modality is currently the gold standard for metabolic evaluation of the left ventricle and recently, it has been suggested that, despite the thinness of the LA wall, LA metabolism evaluation is also feasible using the latest PET camera technologies [7,8].

The last decade has seen the development of PET/CT systems along two axes that led to improvement of the spatial resolution. The first one is the improvement of the timing resolution from about 650 ps in the first time of flight (TOF)-PET/CT commercialized by Philips [9] to about 300 ps and even less in the last TOF-PET generations [10-12] (partially thanks to the use of digital SiPM detectors). The second one is the improvement of dedicated reconstruction algorithms using TOF and point spread function (PSF) information [10-13].

Consequently, in prelude to the prospective study TRIATLON (EudraCT number 2019-001813-17), the purpose of this cardiac phantom study was twofold: first, to compare images quality and uptake quantification obtained on an analog (first generation) and on a digital (last generation) LYSO TOF- PET/CT and, secondly, to determine the most appropriate advanced TOF+PSF reconstruction algorithm to quantify the LA uptake. The methodology was also evaluated clinically on one patient imaged with ^{18}F -FDG on both PET systems.

Materials and Methods

Phantoms

An anthropomorphic Heart/thorax phantom (Radiology Support Devices, Inc, Long Beach, CA, USA) was used, whose liver, heart cavity and walls were filled with typical ^{18}F -FDG activity concentrations observed in patient studies, i.e., 5, 3.8 and 15 kBq/ml, respectively. The heart part of the phantom has only 2 fillable regions: the cavities (about 284 ml) and the walls (about 183 ml excluding the defects volumes). It also includes 2 unremovable defects of about 14 and 42 ml within the walls. The defect located in the interventricular septum (42 ml) was filled with the same ^{18}F -FDG concentration as the heart walls, while the defect in the lateral wall of the left ventricle (14 ml) was only filled with water.

Single-bed position acquisitions of 10 minutes were performed, first using the analog camera (Philips Gemini TF64 TOF-PET/CT - Philips Healthcare, Cleveland OH), 620 ps TOF full width at half maximum (FWHM) and then, immediately after, using the digital one (Philips Vereos TOF-PET/CT - Philips Healthcare, Cleveland OH), 310 ps TOF FWHM.

Reconstruction

List file data were reconstructed with a 2mm voxel size using manufacturer OSEM algorithms with different numbers of iterations and subsets without and with RR. Images were first reconstructed using OSEM algorithms with the recommended manufacturer parameters, i.e. 3 iterations and 33 subsets for the analog camera and 2 iterations and 15 subsets for the digital camera, respectively. As only the digital PET/CT includes a manufacturer PSF RR correction based on the Richardson-Lucy method, a post-reconstruction PSF RR based on the same technique, implemented as a plug-in of the open source ImageJ software [14,15], was also tested on the reconstructed images of both TOF- PET/CT.

The ImageJ RR plug-in DeconvolutionLab2 includes several deconvolution algorithms [15]. We selected the one based on the Richardson-Lucy method that has 2 input parameters: the PSF FWHM that we measured for both PET systems using a ^{18}F point source set at the FOV center, and an iteration number whose default value of 10 was used. In contrary, the manufacturer RR method includes a spatially variant PSF library and has 2 input parameters: a RR iteration number and a regularization factor [13]. For the digital PET, in addition to the manufacturer reconstruction without RR, we performed 3 reconstructions with the PSF RR method by

setting the RR iteration parameter equal to 1, 5 and 10. The regularization parameter was not changed and was equal to 6 in all cases.

Activity recovery assessment

Due to the low dose CT scan, as routinely used for patients, jointly to the close Hounsfield unit values of plexiglass and water, automatic drawing of the volumes of interest (VOI) based on a threshold was not possible. So VOIs were manually drawn around the right (RA) and left atria (LA) and ventricles (RLV) on the CT image. Measured ¹⁸F-FDG activity concentrations in the atria and ventricles walls were compared to exact values to assess the activity recovery.

These CT VOIs were applied on the PET images to assess the walls activity, whatever the PET reconstruction setup (no adaptation of the VOIs to the PET activity was performed) to avoid introduction of bias in the quantitative comparison between reconstructions with and without RR.

Signal to noise ratio assessment

To evaluate and compare the image quality of the PET images, signal to noise ratio (SNR) values were measured from a VOI obtained by using a 9 kBq/ml threshold, i.e. the mean activity concentration of the heart cavity and walls, on the PET original image, i.e. without RR, resulting in a volume including both the atria and ventricles walls. The SNR was calculated by dividing the VOI mean value by its standard deviation (SD).

Patient

To validate the phantom results, one patient of the ongoing prospective study TRIATLON (EudraCT number 2019-001813-17) was acquired on both TOF-PET/CT and these data were analyzed similarly to the phantom data. The TRIATLON study was approved by the Institutional Ethics Committee of Brussels Cliniques Universitaires Saint-Luc, and all patients provided written informed consent.

Single-bed position acquisition of 10 minutes was performed on the Vereos 90 minutes after intravenous injection of about 296 MBq of ¹⁸F-FDG, then repeated directly after on the Gemini. Acquisitions were non-gated and reconstructed with a 2mm voxel size using 3 iterations and 33 subsets for the Gemini and 4 iterations and 15 subsets for the Vereos acquisition, respectively.

As for the actual patient uptake is unknown, the activity recovery and SNR assessments were replaced by the SUV mean and SD measurements of the VOI.

Results

Phantoms

The PET images of the anthropomorphic phantom acquired on the analog and on the digital PET/CT are depicted on Figure 1. The reconstructions without RR already clearly show the better image quality (less noise and better delineation of the walls) provided by the digital TOF-PET/CT (fig 1D) versus the analog one (fig 1A) due to its improved physical characteristics [10,11]. As expected from deconvolution techniques [16], such as the ImageJ plug-in Richardson-Lucy method [14,15] (fig 1B and 1E), the spatial resolution improvement (characterized by the appearance of a thinner wall) is accompanied by an image noise increase, especially in the case of the analog PET/CT (fig 1B). For the digital PET/CT (fig 1F), the manufacturer reconstruction RR algorithm which includes the spatially variant PSF, appears to provide, in 5 iterations, a spatial resolution as good as the ImageJ RR method together with a less noisy image appearance.

As seen on figure 2, VOIs were manually drawn around the right and left atria and around the ventricles walls of the cardiac phantom. The defect located in the lateral wall of the left ventricle and the remaining air bubbles in the phantom walls were excluded from the VOIs.

As we are looking for the best imaging technique for atrial uptake evaluation, we optimized the reconstruction parameters only for the images obtained with the Vereos digital TOF-PET/CT. The convergence of the LA activity recovery as a function of the reconstruction iteration number is displayed on figure 3A. Similar curves are obtained for the RA and RLV activity recoveries with slightly different absolute values (data not shown). For all reconstructions, the convergence of the activity recovery is reached at a product between iterations and subsets of 60. The maximum LA activity recovery increases from about 58% without RR to about 74% with a 10 iterations RR.

Figure 3B shows that the SNR in the digital PET final image is impacted by both the reconstruction and the RR iteration numbers.

We choose as best reconstruction parameters, 4 iterations x 15 subsets for the OSEM algorithm and of 5 iterations for the manufacturer RR algorithm (we will later discuss this choice).

Table 1 illustrates the quantitative impact of the RR correction on the activity recoveries in the right and left atria and ventricles walls and on the image quality for both TOF-PET/CT. Standard reconstruction parameters were used for the Gemini while optimum values were selected for the Vereos. As seen on figure 1, using a RR method leads to an improved spatial resolution, and as a consequence to an improved activity recovery, whatever the TOF-PET/CT considered. However, the SNR, quantifying the image quality, is already worse in the analog PET image without RR and drops strongly after applying the ImageJ RR. Using the selected optimum set of manufacturer RR reconstruction parameters for the digital TOF-PET/CT provides improved activity recoveries of about 70% for the atria and 80% for the ventricles, i.e. about the same as the ImageJ RR method, but with a drop of only 37% of the SNR versus 43% with the ImageJ RR.

Patient

Figure 4 compares the PET images of one patient 18F-FDG cardiac studies on the Gemini and Vereos TOF-PET/CT and reconstructed using OSEM algorithms with the standard 3 iterations and 33 subsets for the Gemini and the optimized 4 iterations and 15 subsets for the Vereos, respectively. Like for the phantom images, the Vereos reconstruction without RR is clearly superior to the Gemini one, as can be seen from the hardly visible left atrium wall and interatrial septum on the Gemini image (fig 4A). On the Vereos images, the atria walls become better defined after RR, with the manufacturer spatially variant PSF method providing the best results in terms of image quality (fig 4F).

Table 2 provides a quantitative analysis of the patient cardiac PET reconstructions. The RR increases the mean SUV but also the SD, as expected from the phantom results (table 1). Like for the heart phantom, the manufacturer spatially variant PSF RR reconstruction available on the Vereos TOF-PET/CT provides the best compromise between the atria uptake improvement and the noise level increase, i.e. highest mean SUV associated with SD values similar to the ImageJ RR.

		Activity recoveries (%)			SNR
TOF-PET/CT	Reconstruction	Left atrium	Right atrium	Ventricles	
Gemini 3 it x 33 subs	without RR	60	63	74	6.8
	with ImageJ RR	73	71	81	3.9
Vereos 4 it x 15 subs	without RR	58	57	72	8.9
	with ImageJ RR	68	66	78	5.1
	with 5 it Philips RR	70	71	80	5.6

Table 1: Activity recoveries for the right and left atria and ventricles walls together with the SNR for the manufacturer reconstructions on the Gemini and Vereos TOF-PET/CT, without RR, with ImageJ RR and, for the Vereos, with the Philips RR.

		Left atrium		Right atrium		Left ventricle	
TOF-PET/CT	Reconstruction	Mean SUV	SD SUV	Mean SUV	SD SUV	Mean SUV	SD SUV
Gemini 3 it x 33 subs	without RR	2.16	0.87	1.95	0.54	11.84	2.92
	with ImageJ RR	2.26	1.45	2.33	1.01	13.49	4.52
Vereos 4 it x 15 subs	without RR	2.13	0.64	2.10	0.59	11.27	2.49
	with ImageJ RR	2.24	1.03	2.37	0.93	12.59	3.68
	with 5 it Philips RR	2.44	0.99	2.50	0.90	13.84	3.71

Table 2: SUV mean and standard deviation (SD) values for the right and left atria and left ventricle walls of a patient cardiac study for the manufacturer reconstructions on the Gemini and Vereos TOF- PET/CT, without RR, with ImageJ RR and, for the Vereos, with the Philips RR.

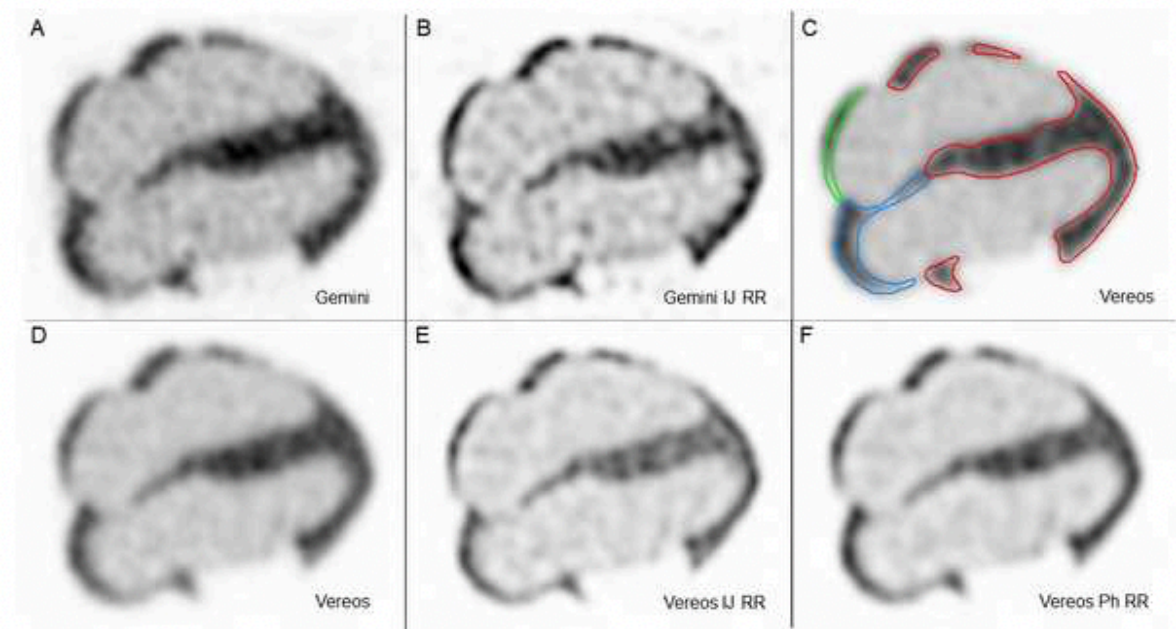


Fig. 1: PET reconstructions of the heart insert of the anthropomorphic phantom. A,B: Gemini system; D,E,F: Vereos system. A,D: manufacturer reconstructions without RR; B,E: manufacturer reconstructions with ImageJ (IJ) RR; F: manufacturer reconstruction including Philips (Ph) RR with 5 iterations/6 regularization; C: manually drawn VOIs around the left atrium (blue), the right atrium (green) and the ventricles (red) shown on the Vereos image.

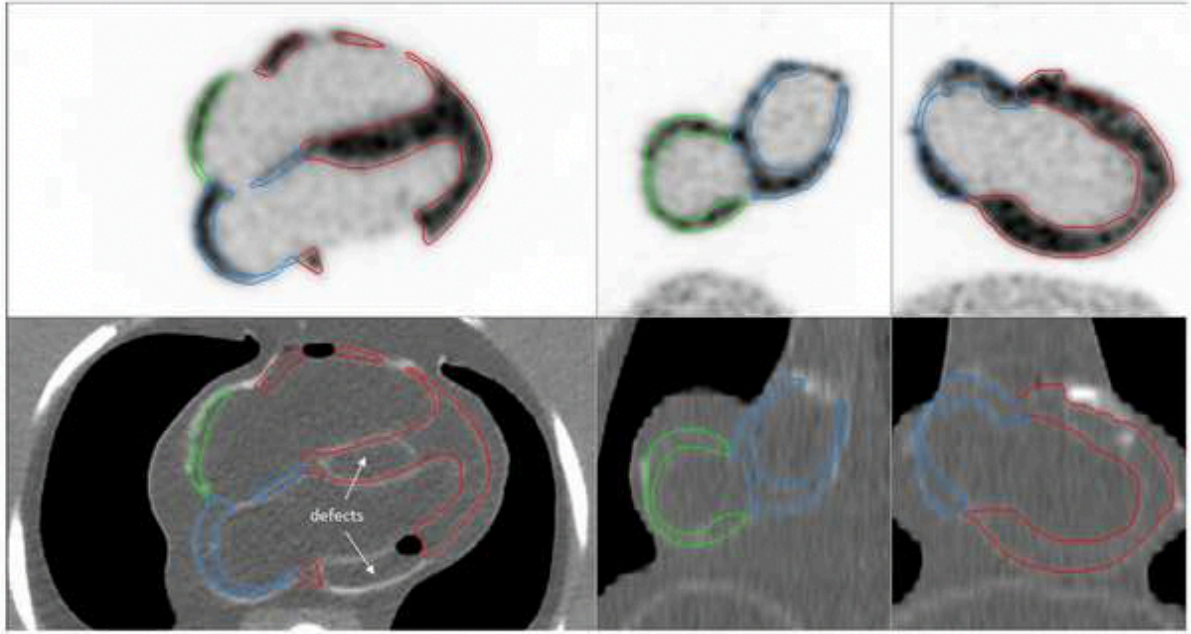


Fig. 2: PET (top row) and CT (bottom row) images of the phantom from the Vereos with VOIs drawn around the left atrium in blue, the right atrium in green and the ventricles walls in red, respectively. Regarding the 2 defects inserts of the phantom, the upper one was filled with the same ^{18}F -FDG concentration as the heart walls, while the other one was only filled with water.

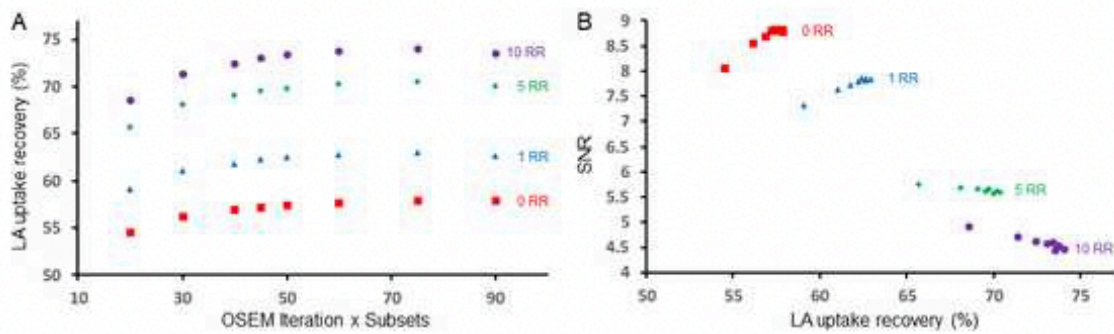


Fig. 3: Activity recovery values for the LA wall as a function of the iteration number of the OSEM reconstruction for the Vereos acquisition. B: SNR value with respect to the LA wall activity recovery. Red squares correspond to the reconstruction without RR (0 RR). Blue triangles, green diamonds and purple circle dots correspond to the reconstruction with the manufacturer RR using 1, 5 and 10 RR iterations, respectively.

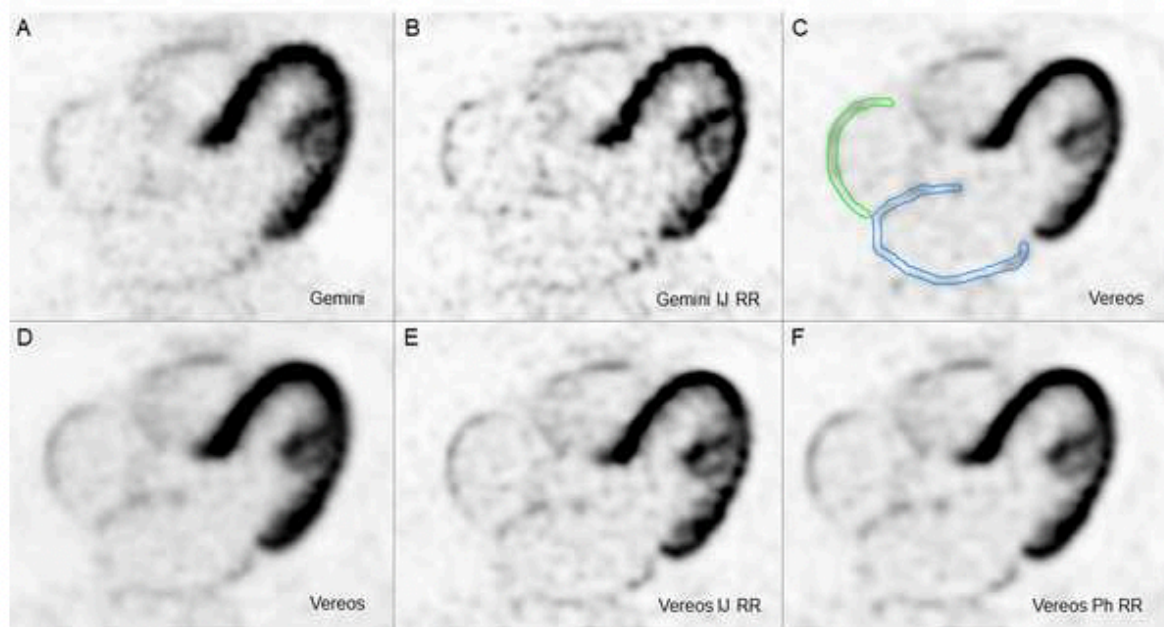


Fig. 4 PET reconstructions of a patient 18F-FDG cardiac study. A,B: Gemini system; D,E,F: Vereos system. A,D: manufacturer reconstructions; B,E: manufacturer reconstructions with ImageJ (IJ) RR; F: optimized manufacturer reconstruction including Philips (Ph) RR with 5 iterations/6 regularization; C: manually drawn VOIs around the right (in green) and left (in blue) atria shown on the standard Vereos image

Discussion

To the best of our knowledge, it is the first time that a phantom study is performed to identify the best reconstruction algorithm to compare the LA uptake in patient 18F-FDG cardiac studies between analog and digital TOF-PET/CT. As the analog TOF-PET/CT system does not include any RR option in the reconstruction algorithm, a third party post-reconstruction RR based on the Richardson-Lucy method was considered (ImageJ DeconvolutionLab2 plug-in).

While this third party post-reconstruction RR method clearly improves the spatial resolution and cardiac walls activity recoveries by using a constant PSF (see figure 1 and table 1), it is not optimized to the PET image specificities like the manufacturer algorithm that includes a RR that takes into account the PSF variations according to the location in the field of view [13]. This results in noisier images, especially in the case of the analog TOF-PET/CT whose original reconstruction is already more impacted by noise (figure 1). Noisier images will result in less reliable activity measurements as they are very sensitive to the VOIs drawing.

Figure 3B shows, for the Vereos TOF-PET/CT, that when no RR or a light RR (only 1 iteration) is performed, the SNR behaves like an increasing function of the LA activity recovery, while for

higher RR iteration numbers, it becomes a decreasing function. This induces that a compromise has to be made between the LA activity recovery and the image reading quality. A post filtering of the image is still possible to make a noisier image more readable. However, one should be careful when pushing the RR algorithms too far (disregarding the SNR) as one might end up with artefactual images that are no more representative of the activity distribution, typically by producing edge artefacts [18,19].

Based on the evaluation of the image quality by our nuclear medicine physicians, we selected as best OSEM reconstruction parameters the values of 4 iterations and 15 subsets as these values correspond to the beginning of the convergence plateau of the activity recovery (see figure 3A), and higher values lead to noisier images. For the manufacturer RR parameter we decided to limit the number of iterations to 5 as the SNR drops quite fast for higher values (see figure 3B). In this study we did not play with the regularization parameter of the manufacturer RR algorithm that was fixed to the recommended value of 6. Optimizing this parameter, whose function is to drive the image smoothness, might still improve the image quality by reducing the noise level but we do not expect it to alter much the optimized set of parameters found in this quantitative study. Together these parameters provide a LA activity recovery of about 70%.

The 18F-FDG cardiac studies performed on both TOF-PET/CT with the same patient confirmed the results obtained with the phantom. Compared to the phantom the patient heart was about 10 percent larger, but ventricular and atrial wall thicknesses were very similar, with values measured on Magnetic Resonance Imaging (MRI) between 0.9 and 1.5 cm for the LV and between 1 and 3 mm for the LA. The limited spatial resolution of the Gemini PET makes it unfit to study the atria metabolism as the atria walls and interatrial septum are hardly seen on the reconstructed images (see figure 4). On the other hand, these structures are already visible on the Vereos reconstruction without RR, and become sharper when using a RR algorithm. The manufacturer reconstruction including the PSF RR still provide a better image quality compared to post-reconstruction RR (see figure 4 and table 2).

Unlike the cardiac phantom filled in the present study with a homogeneous activity distribution in the walls, patients may suffer from pathologies inducing heterogeneities in RA or LA uptake. However, resolution recovery methods tend to reconcentrate the detected

activity in the regions where it originates. If heterogeneities larger than the spatial resolution of the PET system are located in the RA or LA walls, they will still be visible after RR.

One limitation of the present study is that there was no patient motion compensation for breathing and cardiac motions. The heart motion impact on the present results is difficult to evaluate. Using cardiac gating acquisition would help the quantification with the RR method applied on each gated bin separately, and afterwards summing together the activities of the bins in order to recover the non-gated statistics. Without gating the RA and LA walls on the PET image are enlarged by the heart motion. The RR cannot correct for that motion but it will still recover the activity in that enlarged wall, improving the quantification as in that case the VOIs will have to be enlarged too to take the motion blurring into account.

As the reconstruction algorithms with RR, seen as black-boxes by the end user, might strongly differ between manufacturers, the optimized parameters found in this study are only adapted to the Philips Vereos TOF-PET/CT, that is still state-of-the-art system with its 310 ps TOF FWHM. The observed trends for the activity recovery and for the SNR convergences would probably be similar for other systems but this needs to be checked per TOF-PET/CT system in order to extract the best set of reconstruction parameters.

Conclusions

The Philips Vereos TOF-PET/CT images reconstructed with the manufacturer 4 iterations/15 subsets OSEM algorithm including a PSF RR with 5 iterations/6 regularization can be used to quantitatively evaluate the left atrium uptake in ^{18}F -FDG cardiac studies while still preserving image reading quality.

This may lead to more precise evaluation of the metabolic cardiac status of cardiovascular disease, especially when the atria are concerned.

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- CHAPTER III - METHOD AND RESULTS -
ARTICLE 3

Article 3

Altered left atrial glucose metabolism by ^{18}F -FDG-PET in persistent atrial fibrillation normalizes after return to sinus rhythm.

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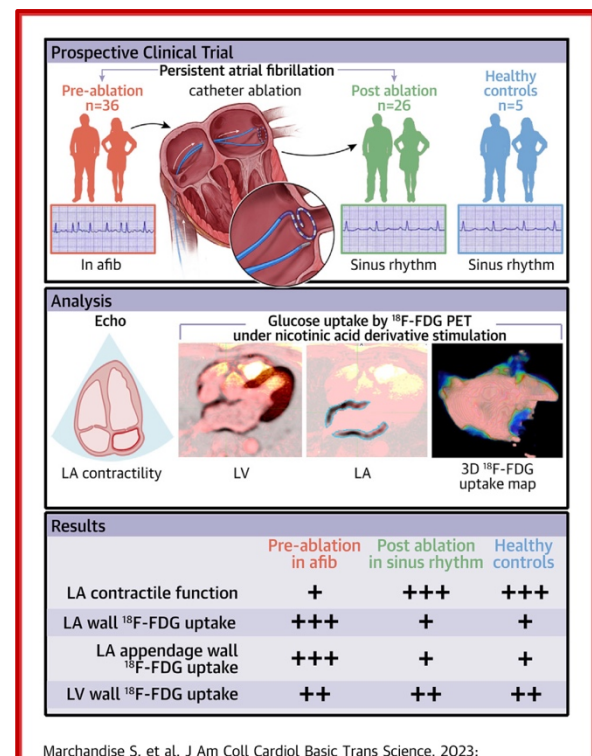
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Abstract:

Background. Few studies evaluated left atrial (LA) metabolism in patients with persistent atrial fibrillation (AF).

Objectives: To evaluate LA glucose metabolism by 18-fluorodeoxyglucose (FDG) Positron Emission tomography (PET) in patients with AF and after return to sinus rhythm.

Method: Thirty-six non-diabetic patients (64 ± 7 years, 29 men) with non-valvular persistent AF undergoing a first AF ablation and 5 healthy age-matched controls (69 ± 5 years, 3 men) without AF underwent FDG PET after administration of a nicotinic acid derivative. Standardized uptake values (SUV) of FDG in the whole LA, its appendage (LAA) and in the left ventricle (LV) were compared to LA ejection fraction and strains by speckle tracking echocardiography. In 26 AF patients the 3 tests were repeated 3 months later after return to permanent sinus rhythm (SR).

Results: Hemodynamic and metabolic parameters were similar in AF patients and controls. With comparable 18F-FDG uptake in the LV, patients in AF exhibited significantly higher mean SUV in LAA (3.5 ± 1.1 vs. 2.5 ± 0.4 ; $p=0.011$) compared to controls. Following a return to SR, LA-SUV (from 2.5 ± 0.7 to 1.9 ± 0.3 , $p<0.001$) and LAA-SUV (from 3.2 ± 1.1 to 1.9 ± 0.6 , $p<0.001$) decreased significantly, whereas the LV-SUV remained unchanged (11.1 ± 5.6 vs 12.2 ± 4.7 $p=0.847$). This occurred despite significant increase of Global Peak Atrial Longitudinal Strain and LA Ejection Fraction and active atrial contraction post-restoration of SR.

Conclusion: LA glucose metabolism is significantly altered in persistent AF and improves after return to SR indicating indicate oxygen wasting and reduced contractile efficiency in AF. These findings support the important role of LA metabolism in the pathophysiology of persistent AF.

Condensed abstract

The role of atrial metabolism alterations for initiation and atrial fibrillation persistence remains poorly understood. Therefore, we evaluated left atrial glucose metabolism by nicotinic acid derivative stimulated 18-fluorodeoxyglucose Positron Emission Tomography in 36 patients with persistent atrial fibrillation undergoing catheter ablation before and 3 months after return to sinus rhythm and compared values against healthy controls. Under identical hemodynamics and metabolic conditions, and while left ventricular FDG uptake remained unchanged, patients in persistent atrial fibrillation presented significantly higher total left atrial and left atrial appendage uptake, which decreased significantly after return to sinus rhythm, despite improvement of passive and active atrial contractile function. These findings support a role of altered glucose metabolism and metabolic wasting underlying the pathophysiology of persistent atrial fibrillation.

Keywords: Atrial Fibrillation, atrial cardiomyopathy, Glucose Metabolism, FDG-PET

Highlights

- AF is characterized by irregular high-frequency excitation and contraction that affect atrial energy demands, resulting in metabolic stress. This metabolic imbalance increases glucose uptake and is associated with the development of LA remodeling which predicts AF persistence.
- Under metabolic conditions which favor glucose utilisation by cardiomyocytes, patients with peAF present increased LA and LAA 18F-FDG uptake relative to healthy controls, while the 18F-FDG uptake in the left ventricle was similar.
- After return to SR, under similar conditions and with similar LV 18F-FDG uptake, LA and LAA FDG uptake decreased significantly, despite improvement of LA contractile function.
- This suggests either higher overall myocardial metabolism and lower myocardial efficiency or metabolic shift to glucose as substrate in AF.

Abbreviations and Acronyms

AF : Atrial Fibrillation
CA : Catheter Ablation
cMR : cardiac Magnetic Resonance Imaging
EF: Ejection Fraction
FAC: Fractional Area Change
FDG : 18-fluorodesoxyglucose
GPALS: Global Peak Atrial Longitudinal Strain
LA : Left Atrium
LGE: Late Gadolinium Enhancement
PET : Positron Emission Tomography
SR: Sinus Rhythm
SUV: Standardized Uptake Value
TBR: Target to background ratio

Introduction:

Atrial fibrillation (AF) is the most common rhythm disorder in clinical practice and its persistent form remains a challenge for the clinician. However, the mechanisms of AF initiation and/or progression to both more persistent forms, remain poorly understood. Structural and functional atrial remodelling, and particularly the development of progressive atrial fibrosis, are well-established hallmarks of AF persistence (1). Experimental studies have also pointed to an important role of atrial metabolic deregulation in AF (2,3). However, so far, there have been few studies evaluating atrial myocardial metabolism in patients in vivo. 18-fluorodeoxyglucose (FDG) Positron Emission tomography (PET) allows for the evaluation of glucose uptake and phosphorylation in the left ventricle (LV) in various diseases (4) and could be a valuable tool for studying LA metabolism in AF. Indeed, through recent improvements in digital PET camera technologies, it is now also possible to quantitatively analyse the 18FDG uptake in the LA (5). Although a few prior studies have described increased atrial FDG uptake in patients with AF (6-10), this was not done under standardized metabolic conditions, which is critical, as glucose uptake is not only dependent on the rate of glucose use of the heart, but also on substrate availability. Oral administration of a nicotinic acid derivative (acipimox)

inhibits peripheral lipolysis reducing plasma levels of free fatty acids and stimulates preferential glucose use by cardiac myocytes (11).

The objectives of the current study were therefore to quantitatively evaluate glucose uptake in non-diabetic patients with persistent AF under well controlled metabolic conditions using FDG PET after nicotine acid administration prior to catheter ablation and to compare them to healthy volunteers and to themselves after return to sinus rhythm.

Methods

Study protocol and population

This prospective trial (TRITALON; EudoraCT reference 2019-001813-17A) was approved by our Internal Review Board (2018/17OCT/389), and written informed consent was obtained from all participants. From January 2020 to September 2022, we identified patients with symptomatic persistent AF referred to our institution for catheter ablation (CA) who met the following inclusion criteria: non-diabetic, aged 18-80 years old, and without prior AF ablation. Exclusion criteria were: hyperthyroidism, renal failure ($\text{GFR} < 30 \text{ ml/m}^2$), infiltrative, hypertrophic or other cardiomyopathies, significant valvular disease, and left atrial appendage (LAA) thrombus as identified on pre-operative transoesophageal echocardiography. The study protocol consisted of a nicotinic acid enhanced atrial ^{18}F -FDG PET scan, cardiac MRI and a transthoracic echocardiogram (TTE) in AF prior to CA. Tests were repeated 3-6 months post-CA in patients which had successfully returned to persistent sinus rhythm for a duration of more than 2 months. A total of 36 AF patients underwent baseline FDG-PET in AF and 26 patients, underwent follow-up PET in sinus rhythm (SR). The study group was compared to 5 healthy, non-diabetic age-matched controls without history of cardiac disease or atrial fibrillation who underwent the same ^{18}F -FDG PET/CT, cMR and TTE protocol.

Cardiac MRI

cMR was acquired using a 3T system (Signa Premier, GE Healthcare). After localizer images, a 3D contrast enhanced angiographic image of the left atrium was acquired after injection of 0.1 mmol/kg Gd-DTPA. Then consecutive cine SSFP short-axis images covering the entire heart and respectively one 2- 3- and 4- chamber long axis images were acquired. Left and right ventricular and atrial end-diastolic and end-systolic volumes and ejection fractions were

computed using Medviso software (Lund Sweden). Late gadolinium images of the ventricle were acquired using 2D single shot inversion recovery images in the same prescriptions. Finally, 20 minutes after contrast injection, atrial fibrosis was evaluated by a prototype ECG-triggered, free-breathing navigator gated high-resolution (1.5x1.5x1.5 mm) 3D whole heart LGE sequence (Hearty®, work in progress GE Healthcare). Images were acquired with optimized trigger time in end-systole with field of view 400 mm, with individual adjustment of the inversion time to optimized nulling of the LA myocardium. LA wall volumes were manually segmented from the DE-MRI images using Slicer3D image processing software (version 4.11.20210226) and the Visualization toolkit library in Python 3.10. Fibrosis by LGE-cMR was evaluated using as reference 2SD of the average intensity of the enhancement around the mitral valve. AF-LGE was classified by Utah stages as I-IV as respectively atrial LGE 0-10%, 10-20%, 20-40% and >40% LGE(12).

Atrial PET imaging

¹⁸F-FDG PET/CT was performed using a high resolution digital 64 slice PET/CT system (Vereos TOF- Philips Healthcare, Cleveland OH) using a previously optimized protocol to enable the reconstruction of high-resolution atrial PET images(5). Patients were studied after overnight fasting and received a nicotinic acid derivative (Acipimox 250 mg) to maximally stimulate myocardial glucose uptake. Prior to tracer injection levels of fasting glucose, insulin, and free fatty acids were measured in venous blood samples. Images were acquired 90 minutes after injection of 300 mBq of ¹⁸FDG using a 10-minute non-gated CT attenuation-corrected scan (voxel size, 2 mm using standard manufacturer OSEM algorithms) and were reconstructed using a 3D ordered-subset expectation maximization algorithm (15 subsets, 4 iterations)

Quantitative measurements of glucose uptake were performed using MIM software (MIM Encore version 7.1.3, MIM Software Inc. Cleveland, OH, USA). PET images were co-registered with contrast enhanced angiographic cMR images and using 3D multiplanar view, the atrial wall was segmented by tracing the epicardial and endocardial contours of the atrium, excluding pulmonary vein ostia and mitral valve annulus (Figure 1a). A mask of the area including these two contours was achieved and allows the construction of a 3-dimensional region of interest (ROI) representing a 3D glucose uptake mapping of the left atrium wall (Figure 1b). Additional ROIs were placed on the left atrial appendage (LAA), left ventricle (LV) and blood pool (for background correction). Atrial glucose standardized uptake value (SUV)

was measured within each ROI as tracer activity (MBq/mL)/injected dose per patient body weight (MBq/kg) after correcting for decay. For each ROI the maximum, minimum, mean and total SUV were measured. The target to background ratio (TBR) was computed for each of LV LA and LAA ROIs as the ratio of the ROI SUV_{mean} to the SUV_{mean} of the cavity blood pool (background). Finally we also computed the mean LA to LV SUV ratio. Inter- and intra-observer reproducibility of measurements were assessed in 3 regions of interest by two operators (SM and QG) in ten randomly selected patients

Trans Thoracic Echocardiography

2D TTE was acquired using an EPIC sonography system and stored on a Intellispace PACS system (both Philips Healthcare, Andover, MA, USA). Images were analyzed offline by one observer (SM) and all measurements were performed by averaging 3 cardiac cycles as described before(13). LV volumes and ejection fraction were calculated using Simpson's biplane method. The E/e' ratio was calculated from peak mitral flow E and the average of septal and lateral e' tissue Doppler velocities. LA volume and strain analysis were performed on dedicated apical 4- and 2-chamber views of the LA acquired with a frame rate between 60 and 80 frames per second and analyzed using Image-Arena™ cv4.6 (TomTec Imaging Systems, Unterschleissheim, Germany) in duplicate by two experienced blinded echocardiographers (SM and QG). Maximal and minimal indexed LA volume were measured respectively at the end of LV systole and LV diastole and indexed to body surface area. Fractional area change (FAC) and ejection fraction (LAEF) of passive emptying fraction were computed respectively, as the percentage ratio of change of LA area and volume during systole. We also computed Reservoir Global Peak Atrial Longitudinal Strain (GPALS) conduit (LAScd) and contraction phase (LASct) strains. All strains were computed using LV end-diastole as zero-strain point. LASct was only computed when patients had returned to SR.

Electroanatomical mapping and catheter ablation procedure

Electroanatomic mapping of the LA was obtained using the ConfiDENSE™ CARTO3 system v6.0.70 using the 2515 Variable Loop Lasso Multi-Electrode Eco Nav (Biosense Webster, Diamond Bar, CA) using at least 1000 measurements as described before (13). Electrical cardioversion was attempted after an initial mapping, and mapping was repeated in sinus rhythm. Low voltage area was defined as bipolar peak-to-peak voltage amplitude of < 0.5 mV

in sinus rhythm and < 0.31 mV in AF. All patients underwent radiofrequency PVI with additional lines or Complex Atrial Fractionated Electrogram (CAFE) ablations performed at the physician's discretion.

Statistical analysis.

All analyses were performed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, United States) and R software version 3.5 (R-project, Vienna, Austria) and a p-value $p < 0.05$ was considered statistically significant. Our study had 80% power with 26 patients to demonstrate a mean SUV change of 0.78 ± 1.03 between baseline and follow-up using a paired t-test, and to demonstrate a mean SUV difference of 0.55 ± 0.80 between 36 AF patients and 5 controls using an unpaired t-test. Continuous values were evaluated for normality using QQ-plots, histograms, and the Kolmogorov-Smirnov test, and are expressed as the mean $\pm$ standard deviation (SD) or the median with interquartile range (IQR) depending on their distribution. These values were then compared between patients and controls, respectively, using the two-sided t-test or the Mann-Whitney U test, while individual data in patients before and after return to SR were compared either with the paired t-test or the Wilcoxon signed-rank test. Categorical data are expressed as counts and percentages and were compared using the chi-squared test. The relationship between PET parameters, LVA or echocardiographic parameters was evaluated by linear regression analysis and the Pearson correlation coefficient. Intra- and inter-observer reproducibility of SUV measurements was analyzed using the coefficient of variation (CV) and intraclass correlation coefficient (ICC) with 95% confidence interval (CI) for agreement.

Results

Patient characteristics

Table 1 presents the baseline characteristics of the AF patients and healthy volunteers. The AF patients were predominantly male ($n=29$, 80.6%) with an average age of 64.3 ± 6.9 years and the average duration of AF since first diagnosis was 4.7 ± 4.0 years. Nineteen patients (52.7%) patients had AF persisting longer than 6 months and 8 (22.2%) > 1 year. The median EHRA score was 2 IQR [1] and the median CHADS-VASC score 2 IQR [2]. Three (15.0%) patients

had a history of congestive heart failure and 5 (13.8%) had had a transient ischemic attack, stroke or thromboembolic event. Seven patients (19.4%) had coronary artery disease; 4 had suffered from a myocardial infarction. In terms of medical treatment 24 (66.7%) patients were treated with betablockers, 3 (8.3%) received sotalol, 9 (25.0%) amiodarone and 6 (16.7%) a Class I antiarrhythmic drug. All but one patient received direct oral anticoagulation. Ten (27.8%) patients received statins. No patient was treated with metformin or other antidiabetic drugs.

No statistically significant discrepancies were observed between AF patients and healthy volunteers in terms of sex, age, and weight. The patients exhibited a tendency for higher BMI than controls, along with significantly greater prevalence of cardiovascular risk factors (e.g. hypertension and smoking). At the time of the study, systolic blood pressure, estimated GFR, glycemia, insulinemia, did not differ significantly between patients and controls. Notably, no patient had hyperglycaemia > 110 mg/dl. All AF patients had adequate control of resting heart rate (< 110 bpm); nevertheless, heart rate was slightly but significantly higher in patients than in controls. Echocardiographic and CMR left, and right ventricular volumes and ejection fraction was similar, but the LA diameter and volume was higher in AF patients than in controls. No patient had LGE in the myocardium or any indication for infiltrative disease (amyloidosis / sarcoidosis). The average atrial LGE extent was $11.7 \pm 9.5\%$ (range 0.0-45.1%). Nine patients were considered to have Utah stage I, 19 Utah stage II and the remaining 6 patients presented with extensive atrial fibrosis (Utah stage III or IV). After PVI ablation, LGE was non-significantly different ($14.3 \pm 8.8\%$, $p=0.273$). By electroanatomical mapping the low voltage area represented $7.4 \pm 6.8\%$ of the entire atrium.

Atrial function and FDG uptake in patients during permanent AF vs controls

Table 2 summarizes data on atrial function and FDG uptake in patients with AF, and in healthy volunteers. As expected, atrial functional parameters (FAC, EF and LA strains) were significantly lower in persistent AF patients than in controls. The F18 dose injected (7.9 ± 0.5 vs 7.7 ± 0.5 mCi $p=0.974$), the delay to acquisition (96.9 ± 9.2 vs 96.0 ± 5.6 min, $p=0.126$) and the acquisition duration (10.4 ± 1.8 vs 10.0 ± 0.1 $p=0.183$) were similar among patients and controls. The image quality was high in all but one exam, likely due to an issue with the injection. This enabled accurate identification of all the atrial segments, including the left atrial appendage (LAA) in 97.2% of exams. While the ^{18}F -FDG uptake was similar in the LV wall in AF patients

as in healthy controls, AF patients had significantly higher ^{18}F -FDG uptake in the LA wall and particularly in the LAA than controls. Hence the ratio of mean SUV of the LA to LV and LAA to LV was significantly higher in AF than in controls (Figure 2).

Changes of FDG uptake and contractile function after return to sinus rhythm

All patients successfully underwent CA. CA consisted of PV ablation in all patients and additional lines or Complex Atrial Fractionated Electrogram (CAFE) ablations in 8 (22.2%) patients. The data of the 26 patients undergoing repeat FDG PET post-ablation are shown in Table 3 and in Figure 3. The repeat exam was performed on average 4.4 ± 1.8 months (range 3-8 months) after CA and return to SR. All patients were in SR for more than 2 months at the time of the repeat exam. A significant increase was not observed in cMR LGE in LA after ablation, except for the lesions in ostia of the pulmonary veins which were not included in PET ROI measurements. Hemodynamics and metabolic conditions were not significantly different in SR as compared to persistent AF, except for heart rate which was slightly lower in SR than in persistent AF. LVEF was higher in the control group. This difference was weak while the LV strain was significantly better. There were also no differences in injected FDG dose injection (7.9 ± 0.5 vs 7.9 ± 0.5 mCi $p=0.974$), delay to acquisition (98.1 ± 9.6 vs 95.2 ± 7.9 min, $p=0.228$) and the acquisition duration (10.6 ± 2.1 vs 10.0 ± 1.0 $p=0.185$). Also, patient treatment was not significantly different especially for β -blockers ($p=0.327$) and angiotensin receptor blockers or angiotensin-converting enzyme inhibitors ($p=0.161$)

An example of a typical PET study of a patient in persistent AF and after return to SR is shown in Figure 4, while the individual changes of LA contractile function and FDG uptake SUV in LA are shown in Figure 3. Patients significantly improved passive (FAC, LAEF and LASr) and regained active atrial function (A wave velocity and LASct) which was previously absent. This occurred while on average the mean SUV ^{18}F -FDG uptake in LA and LAA decreased respectively by 20.4% and 34.1%, and in the absence of significant change in mean SUV uptake in the LV. Therefore, the average LA/LV and LAA/LV FDG uptake also significantly decreased. The decrease of LA FDG uptake was present in all patients, but we could not observe direct relation to LA low voltage area or LGE. However, despite a reduction of FDG uptake in patients in SR, relative atrial FDG uptake (mean LA to LV SUV ratio) remained slightly higher than that of volunteers, while the absolute atrial uptake value was non-significantly lower. Figure 5 and

6 show examples of 3D 18F-FDG uptake maps of the LA and corresponding electroanatomical maps. Homogenous FDG uptake as observed in most patients, correlated with normal electroanatomical maps (Figure 5), whereas areas of reduced FDG uptake spatially accorded with areas of low electrical voltage and scarring (Figure 6).

Reproducibility of measurements

Intra- and inter-observer variability analysis of SUV measurements in LA, LAA and LV found the reproducibility was high with ICC measures ranging from 0.87 to 0.99, as detailed in Table 4.

Discussion

The principal findings of our present study can be summarized as follows:

1. Under metabolic conditions which favor glucose utilization by myocytes, patients with persistent AF present with increased relative LA/LV ratio and especially increased LAA and LAA/LV 18F-FDG uptake as compared to healthy controls.
2. After return to SR, under similar conditions and with similar LV 18F-FDG uptake, LA and LAA FDG uptake decreased significantly, despite improvement of LA contractile function.

Better understanding the pathophysiology of persistent AF is important due to the heightened risk of cardiovascular morbidity and mortality associated with the condition. PET offers an ideal means of assessing myocardial metabolism in vivo. Recent improvements in PET technology have enabled higher spatial resolution and improved image quality, thereby allowing for the acquisition of high-quality PET images of the atria without influence of partial volume effect(5). Our study is novel in that it prospectively utilized this technique to explore the metabolic changes in the atria of patients with persistent atrial fibrillation (persistent AF) in comparison to those with restored sinus rhythm. Although some previous studies have reported increased FDG uptake in atria of patients with atrial fibrillation (6-10), the type of AF (ie paroxysmal vs persistent varied) and importantly these studies were not performed under well standardized metabolic conditions, but usually only after fasting. Indeed, considering the metabolic conditions is primordial when interpreting FDG uptake of the heart and surrounding tissues, as myocardial metabolism preference is heavily reliant on substrate availability.

Therefore, the interpretation of the increased FDG signal in earlier work was complicated. Generally, increased FDG uptake has been attributed to the presence of inflammatory cells, such as macrophages and lymphocytes, either in the myocardium or in adjacent epicardial adipose tissue, or both (7). The unique and significant contribution of our study is the evaluation of a uniform cohort of non-diabetic patients with persistent AF after administration of a nicotinic acid derivative. Nicotinic acid significantly inhibits lipolysis, thereby reducing plasma free fatty acid concentrations and favouring glucose utilization by myocytes. This approach enabled us to acquire high-quality 3D PET images in both patients and controls. Furthermore, co-registration with cMR angiographic images allowed for addressing partial volume effects and enabled accurate localization of FDG uptake to the atrial wall, the fossa ovalis, mitral annulus, pulmonary vein ostia, and importantly the intraatrial septum and LAA. As these latter structures are not encircled by fatty tissue, this strongly suggests that FDG uptake originated from the atrial myocardium, rather than epicardial fat. Moreover, FDG uptake was also detected in healthy subjects without AF, albeit at slightly lower levels, and was found to be relatively homogeneous throughout the atria without any indication of focal uptake, suggesting that inflammation is unlikely to be involved, which is consistent with other reports(9). Intriguingly, uptake in the LAA was higher than in the remaining LA, potentially indicating the higher vulnerability of the LAA to AF. Although we cannot definitively rule out an inflammatory contribution, we thus believe that the increased FDG signal observed in our study likely originated from atrial myocytes. Changes in myocardial FDG uptake could potentially also be attributed to hemodynamic and pharmacological factors, such as antiarrhythmic drugs or beta blockers. However, no discernible changes in these factors were observed before and after the reversion to sinus rhythm. Furthermore, no significant differences in FDG uptake in the left ventricle were observed between AF after the return to SR. Therefore, we do not believe that these factors are responsible for the alterations in atrial FDG uptake that transpired after the reversion to SR. We also conducted a comprehensive multimodality evaluation of atrial structure and function, by LGE-cMR and electroanatomical voltage mapping, which revealed that, despite prolonged persistent AF, most of the atrial tissue was still largely viable and not infarcted. This was further corroborated by speckle tracking echocardiography, which demonstrated a return to mechanical activity following restoration of SR. Since CA only resulted in minimal scarring increase, mainly in the pulmonary veins, which were excluded from PET ROIs and since the SUV decreased also strongly in the

LAA, which was not approached during CA, we do not believe that increase of atrial scarring could have contributed to decrease of FDG uptake after return to SR.

We thus believe that our results are most consistent with either atrial metabolic wasting and overall increase of atrial oxidative metabolism, or with a metabolic shift to the preferred glucose use in atrial myocytes during persistent AF, which normalized in SR. Both could be directly implicated in the pathophysiology of the disease. Indeed, AF is characterized by the continuous, irregular, and rapid electrical activity of multiple wavelets of electrical re-entry in the atria, resulting in increased rates of action potential depolarization, ion flux, and myocellular calcium overload of the atrial myocytes with enhanced rates of activation of myofilaments (14), which are however mechanically inefficient. The increased myocardial workload caused by the persistent contraction of the cardiomyocytes can lead to increased energetic demands in AF (15). Additionally, evidence suggests that the chaotic atrial activity of AF affects the normal metabolic pathways of the myocardium, modify GLUTs trafficking, leading to changes in the utilization of substrates for energy production in order to sustain the increased energy consumption due to the heightened workload and maintenance of the arrhythmia. This is suggested by animal models showing that oxidative stress experienced during AF may lead to alterations of mitochondrial function (16), and that AF may result in reduced ATP synthesis and a metabolic shift from metabolic switch from fatty acid beta-oxidation to glucose uptake, increased anaerobic glycolysis and lactic acid production, AMPK activation, changes in Glucose transporter expression, GLUTs trafficking and structural remodelling of the atrium (17), with increased glycogen accumulation and reduced myofilaments, mimicking those observed in ventricular myocytes from chronic hibernating myocardium (18). It is also supported by microarray probes showing alterations of mRNA expression transcriptome in atrial tissue (19,20) in humans. All these paradigms support the existence of an atrial cardiomyopathy (21) where altered atrial metabolism, is a key component of both AF initiation and progression. Indeed, the metabolic wasting might lead to ischemia, resulting in myocyte necrosis and apoptosis and subsequent replacement of the tissue by fibrosis. To our knowledge, our study is the first study to directly support such metabolic alterations in atrial cardiomyopathy by FDG imaging in patients with persistent AF. Further work is required to even better understand the underlying mechanisms of such increased FDG uptake in AF. Ideally, to understand which mechanism (increased metabolism, tissue hypoxia, ischemia or inflammation) is prevailing, it would have been interesting to also

have FDG data in fasted state only in the same patients, this was however not feasible due to complexity of study design and radiation exposure.

Clinical Implications

Besides providing further insights into the pathophysiology of AF, our study demonstrates the feasibility of acipimox-enhanced FDG PET for high-quality atrial imaging in vivo. This technique may be comparable to cMR LGE and other imaging techniques, potentially providing clinical applications in evaluating atrial remodelling and viability prior to CA (19). FDG-PET uptake could serve as an indication of preserved atrial myocyte function, thereby demonstrating the absence of atrial fibrosis. Further research should investigate the potential utility of this non-invasive imaging technology in clinical practice and evaluate the correlation between FDG-PET uptake and atrial fibrillation (AF) structural remodelling or AF duration, in order to guide AF ablation strategies and predict the outcomes of pulmonary vein isolation procedures.

Limitations

This single-center study had a relatively small sample size and evaluated only semiquantitative atria FDG standard uptake values, but not quantitative glucose uptake due to the lack of a ^{18}F input curve. No adjustments were made for multiple testing to preserve type I error, thus results should be interpreted with caution. We did not perform a test-retest reproducibility of FDG SUV under acipimox in healthy volunteers, nor a 2nd FDG study under fasted conditions alone, due to concerns for radiation exposure. Variability in lipolysis response to nicotinic acid derivatives, and associated effects such as vasodilatation and increase of myocardial perfusion could theoretically have influenced acipimox induced stimulated glucose uptake. Actual glucose transport rate could also differ from FDG uptake rates in the case of variability of the FDG/glucose transport rate through GLUT transporters, known as the so-called lumped constant. Also, we were unable to differentiate between atrial glucose and total oxidative metabolism, which would require dynamic ^{11}C acetate PET imaging.

Conclusions

Using nicotinic acid stimulated PET we observed significantly increased ¹⁸F-FDG uptake in the LA wall during persistent AF relative to healthy controls, which significantly normalized after return to SR. These results indicate augmented glucose and overall atrial myocardial metabolism, as well as reduced atrial contractile efficiency and energy wasting in persistent AF compared to SR. These findings suggest that metabolic changes may be implicated in the perpetuation and development of persistent AF.

Clinical Perspective

Competencies in Medical Knowledge

Nicotinic acid stimulated PET showed increased FDG uptake in patients with persistent atrial fibrillation relative to healthy controls, which normalized after return to sinus rhythm.

These findings support either metabolic shift or overall oxidative wasting in persistent atrial fibrillation.

Translational Outlook

Further studies using PET will allow us to better understand the metabolic alterations underlying atrial fibrillation and atrial cardiomyopathy. Furthermore, FDG-PET might have value to non-invasively detect atrial viability prior to ablation treatment.

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Tables

Table 1 Characteristics of the study population

	AF patients (n=36)	HV (n=5)	P value
Clinical Parameters			
Age (years)	64.3±6.9	68.9±4.8	0.114
Sex (M/F)	29/7	3/2	0.457
Weight (kg)	88.1±9.6	76.0±13.9	0.127
BMI (kg/m ²)	28.9±3.5	24.8±3.3	0.052
CV risk factors			
Hypertension	14 (38.9)	0	<0.001
Hypercholesterolemia	18 (50.0)	4 (80.0)	0.220
Diabetes	0 (0)	0 (0)	/
Family History of CAD	13 (36.1)	2 (40.0)	0.886
Smoking	11 (30.6)	0 (0.0)	<0.001
Hemodynamic and metabolic parameters			
SBP (mmHg)	127.6±10.9	129.0±5.4	0.663
HR (BPM)	84.0±13.5	71.0±7.4	0.081
Glycemia (mg/dl)	98.8±13.8	96.0±6.8	0.480
Insulinemia (mIU/L)	69.5±36.5	65.3±3.0	0.804
eGFR (ml/min)	70.5±14.5	81.0±12.9	0.156
Echocardiographic parameters			
LVEF (%)	58.5±9.3	64.2±5.6	0.092
LA diameter (mm)	46.9±5.2	38.6±6.7	0.047
LA volume (ml/m ²)	59.3±18.0	17.5±3.5	<0.001
cMR parameters			
LVmass indexed (g/m ²)	56.9 [13.4]	46.5 [17.2]	0.202
LVEDVi (ml/m ²)	75.2 [19.2]	62.2 [14.8]	0.024
LVEF (%)	50.8±8.1	56.7±3.5	0.072
RVEDVi (ml/m ²)	74.8±14.2	60.2±19.6	0.022
RVEF (%)	51.7±8.1	57.5±9.1	0.145

Table 1: Data are presented as mean±SD, number (percentage), or median (interquartile range). AF: atrial fibrillation; HV: healthy volunteers; BMI, body-mass index; CAD, coronary artery disease; SBP, systolic blood pressure; HR, heart rhythm; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LA, left atrium; LV, left ventricle; LVEDVi, left ventricle end diastolic volume indexed; RVEDVi, right ventricle end diastolic volume indexed and RVEF, right ventricular ejection fraction.

Table 2: atrial function and metabolism in persistent AF vs healthy volunteers

	<u>persistent</u> <u>AF (n=36)</u>	<u>HV</u> <u>(n=5)</u>	<u>P value</u>
FAC (%)	13.8±6.1	37.0±5.4	<0.001
LAEF (%)	19.8±8.2	47.7±7.7	0.004
GPALS (%)	8.8±3.5	28.3±4.9	<0.001
LV SUV mean	11.4±5.1	14.6±3.5	0.115
LA SUV mean	2.9±0.8	2.6±0.3	0.151
LA/LV ratio	0.3±0.2	0.2±0.0	0.002
LAA SUV mean	3.5±1.1	2.5±0.4	0.011
LAA/LV ratio	0.4±0.2	0.2±0.0	<0.001

Table 2: Data are presented as mean±SD. P value expresses the difference between healthy volunteers (HV) and persistent AF patient during AF. FAC denotes fractional area change; LAEF, left atrial ejection fraction; GPALS, global peak atrial longitudinal strain; LA, left atrium; LAA, left atrial appendage; LV, left ventricle and SUV, standardised uptake value.

Table 3: Hemodynamics, atrial function and metabolism in persistent AF (pe AF), after return to sinus rhythm (SR) and in healthy volunteers (HV).

	pe AF (n=26)	SR (n=26)	HV (n=5)	P value (AF vs SR)	P value (SR vs HV)
HR (bpm)	80.9±17.6	62.3±10.5	71.0±7.4	<0.001	0.056
SBP (mmHg)	126.4±10.6	130.6±7.9	129±5.4	0.205	0.634
Glycemia (mg/dl)	97.6±13.9	92.8±9.3	96.0±6.8	0.070	0.394
Insulinemia (mIU/L)	59.6±39.9	69.2±43.5	65.3±3.0	0.605	0.783
FFA (mg/dl)	142.0±41.1	120.9±52.7	NA	0.419	NA
LVEF (%)	59.6±9.5	54.8±2.2	64.2±5.6	0.664	0.136
LV aGLS	NA	15.5±0.7	18.1±0.5	NA	<0.001
E wave velocity (cm/s)	75.5±20.0	62.4±21.4	65.4±13.9	0.028	<0.001
A wave velocity (cm/s)	NA	58.2±9.8	75.4±18.2	NA	<0.001
Average e' (cm/s)	9.6±2.9	7.8±1.8	7.1±0.7	<0.001	0.022
E/e' (%)	8.9±3.8	8.1±2.7	9.2±1.6	0.241	0.141
FAC (%)	13.9±6.2	25.4±6.8	37.0±5.4	<0.001	0.004
LAEF (%)	19.9±8.4	33.5±9.3	47.7±7.7	<0.001	0.001
LASct (%)	NA	7.3±3.0	15.2±4.1	NA	0.001
LAScd (%)	NA	10.2±5.1	13.1±2.1	NA	0.045
LASr (%)	8.8±3.5	17.3±2.2	28.3±4.9	<0.001	0.003
LV SUV mean	11.1±5.6	12.2±4.7	14.6±3.5	0.847	0.668
LA SUV mean	2.9±0.9	2.2±0.4	2.6±0.3	<0.001	0.035
LA/LV ratio	0.4±0.2	0.2±0.1	0.2±0.0	0.018	0.339
LAA SUV mean	3.2±1.1	2.1±0.6	2.5±0.4	<0.001	0.118
LAA/LV ratio	0.4±0.3	0.2±0.1	0.2±0.0	0.001	0.306

Table 3: Data are presented as mean±SD. LA: Left Atrium; LAA, left atrial appendage; LV, left ventricle; SUV, Standardised Uptake Value; SBP, systolic blood pressure; HR, heart rhythm; FFA: free fatty acid; LVEF, Left Ventricle Ejection Fraction; LV aGLS: Left Ventricle absolute Global Longitudinal Strain; LAEF, Left Atrial Ejection Fraction; FAC, Fractional Area Change; LASct, Left Atrial Strain contraction; LAScd, Left Atrial Strain conduit; LASr, Left Atrial Strain reservoir and NA, not applicable.

Table 4: Intra-observer and inter-observer variability analysis

	Intra-observer		Inter-observer	
	CV	ICC	CV	ICC
LA SUV	1.3±3.6	0.98 [0.95-0.99]	1.2±2.3	0.97 [0.75-0.99]
LAA SUV	-8.1±32.9	0.96 [0.86-0.99]	5.0±7.8	0.87 [0.71-0.99]
LV SUV	-0.8±6.6	0.98 [0.93-0.99]	9.2±4.1	0.99 [0.88-0.99]

Table 4: Coefficient of variation (CV) is presented as a percentage (mean±SD) and intraclass correlation coefficients (ICC) with 95% confidence interval (95% CI). LA denotes Left Atrium; LAA, left atrial appendage; LV, left ventricle; SUV, Standardised Uptake Value.

Figure legends

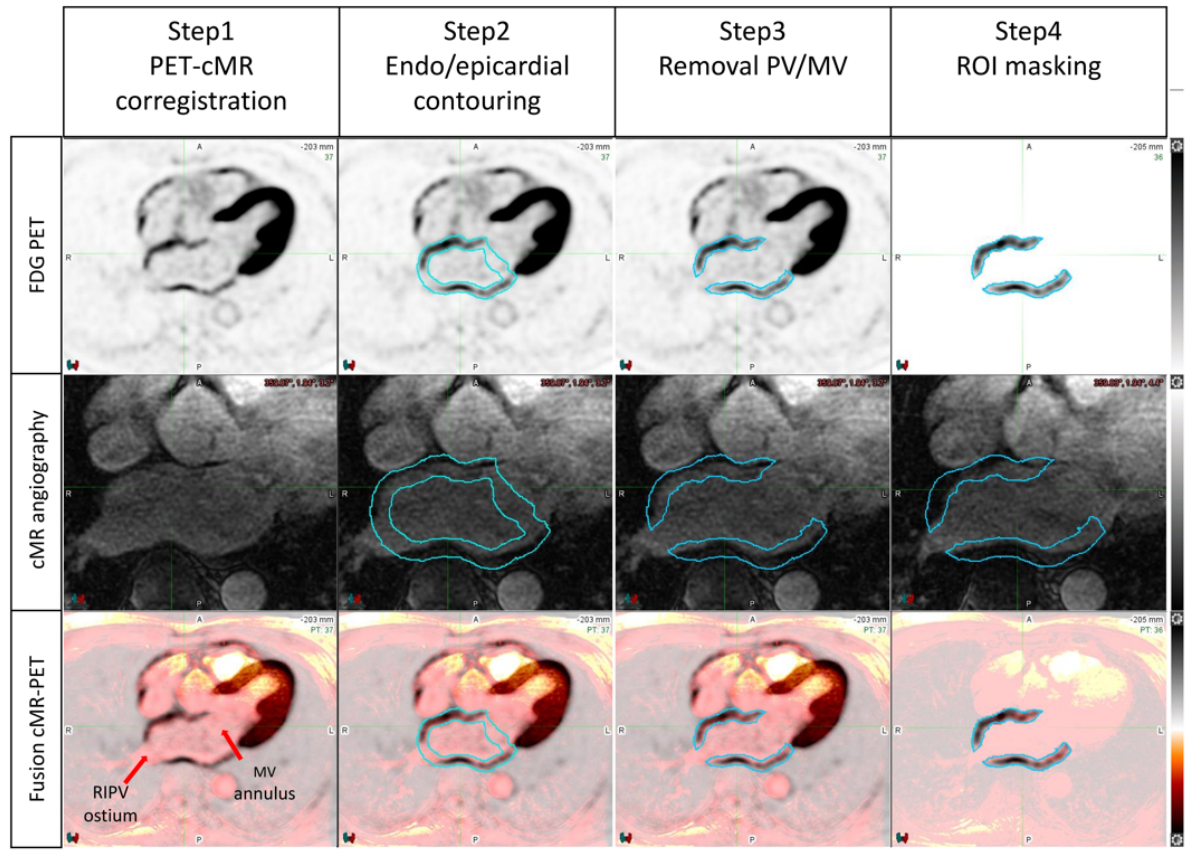


Figure 1a: Workflow of segmentation and postprocessing of left atrial ^{18}F FDG-PET images.

PET images were coregistrated with cMR angiographic images. Then a mask of the inner and outer contours of the LA was manually defined on cMR angiographic images, pulmonary veins and mitral valve were cut and the mask was copied to the PET images. This allowed definition of a 3D ROI of the FDG uptake of the LA wall. RIPV: Right Inferior Pulmonary Vein, MV: Mitral Valve.

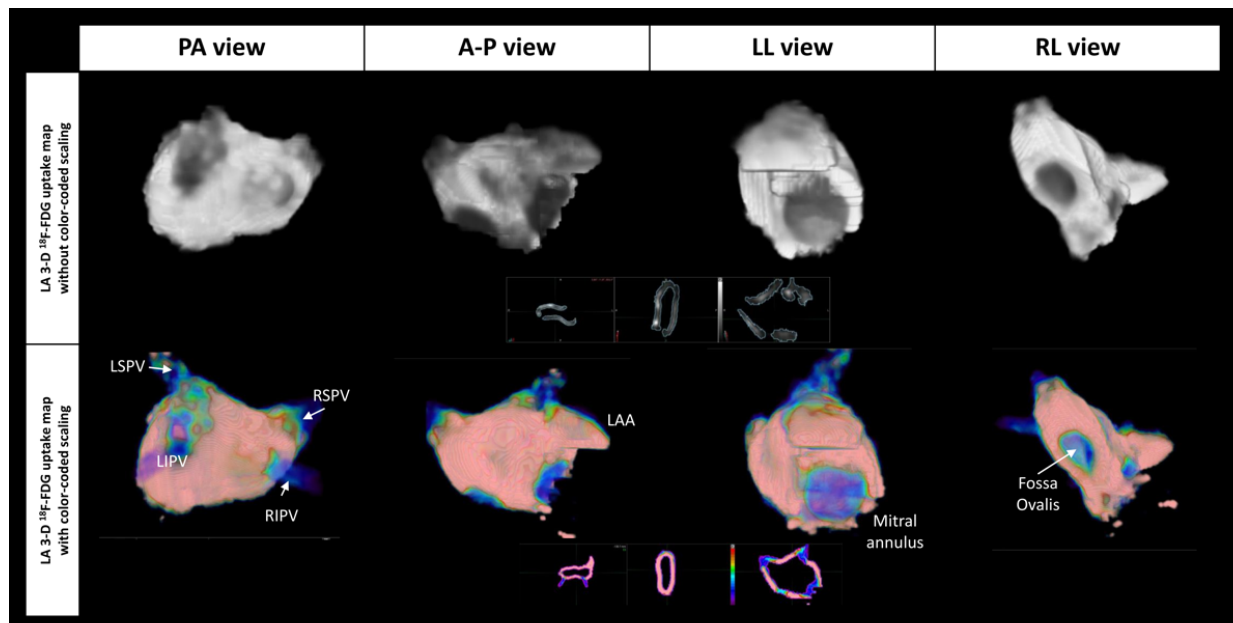


Figure 1b: Rendered 3D volumetric model of the left atrium, before (top) and after (bottom) color coded for maximum ^{18}F -FDG SUV intensity from different views.

Labels identify atrial anatomic structures: LSPV: Left Superior Pulmonary Vein; LIPV: Left Inferior Pulmonary Vein; RSPV: Right Superior Pulmonary Vein; RIPV: Right Inferior Pulmonary Vein, LAA: Left Atrial Appendage.

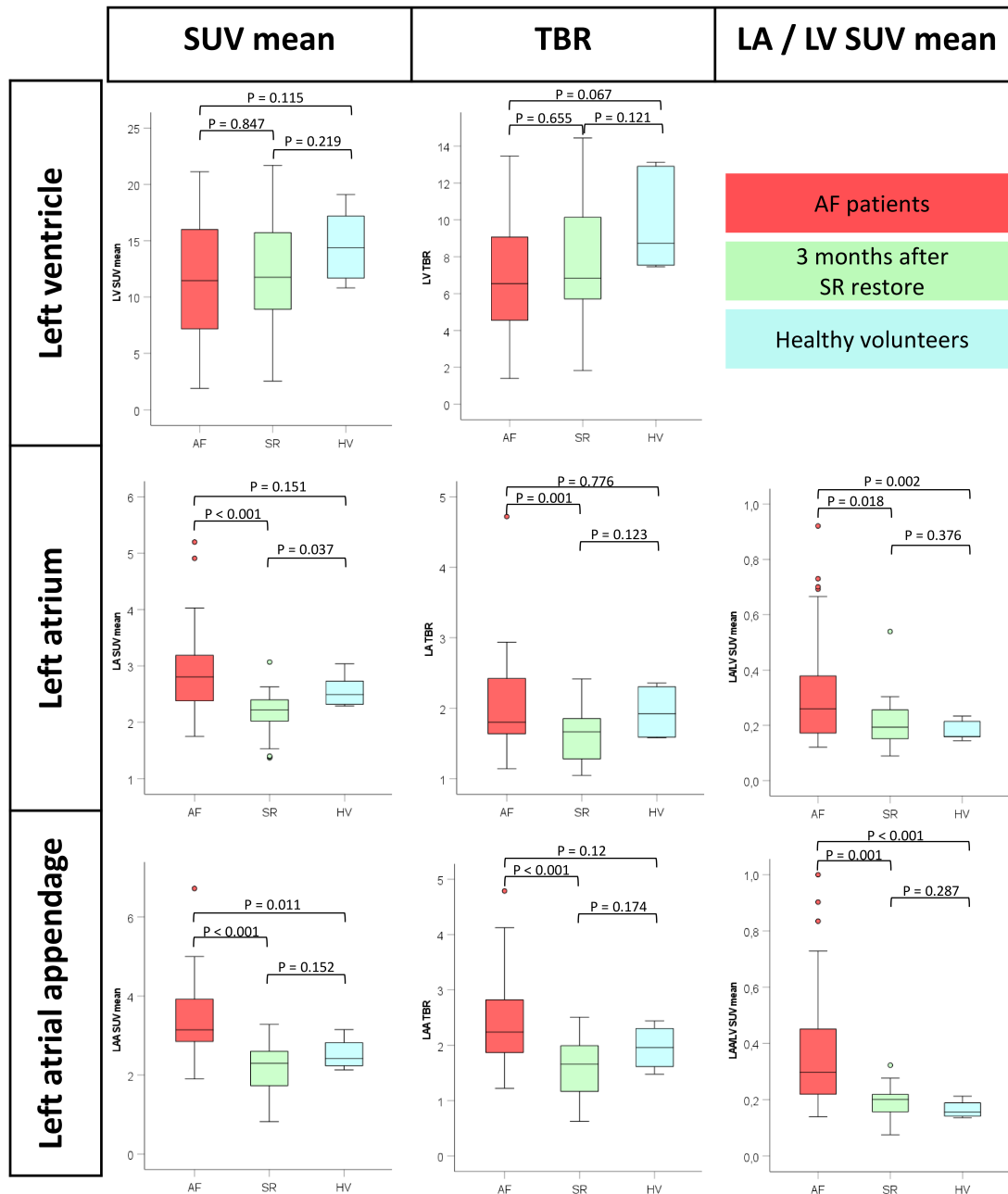


Figure 2: Difference in FDG uptake parameters between persistent atrial fibrillation patients, 3 months after sinus rhythm restore and healthy volunteers in 3 region of interest. Box Plot showing difference in mean Standardised Uptake Value (SUV), Target to Background Ratio (TBR) and LA/LV SUV mean ratio between persistent atrial fibrillation (AF) Patients, 3 months after Sinus Rythm (SR) restore and Healthy Volunteers (HV) in 3 region of interest (Left ventricle (LV), left atrial (LA) and left atrial appendage (LAA)). The box represents interquartile range, the line within the box indicates the median value, whiskers show minimum/maximum values. * represent $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

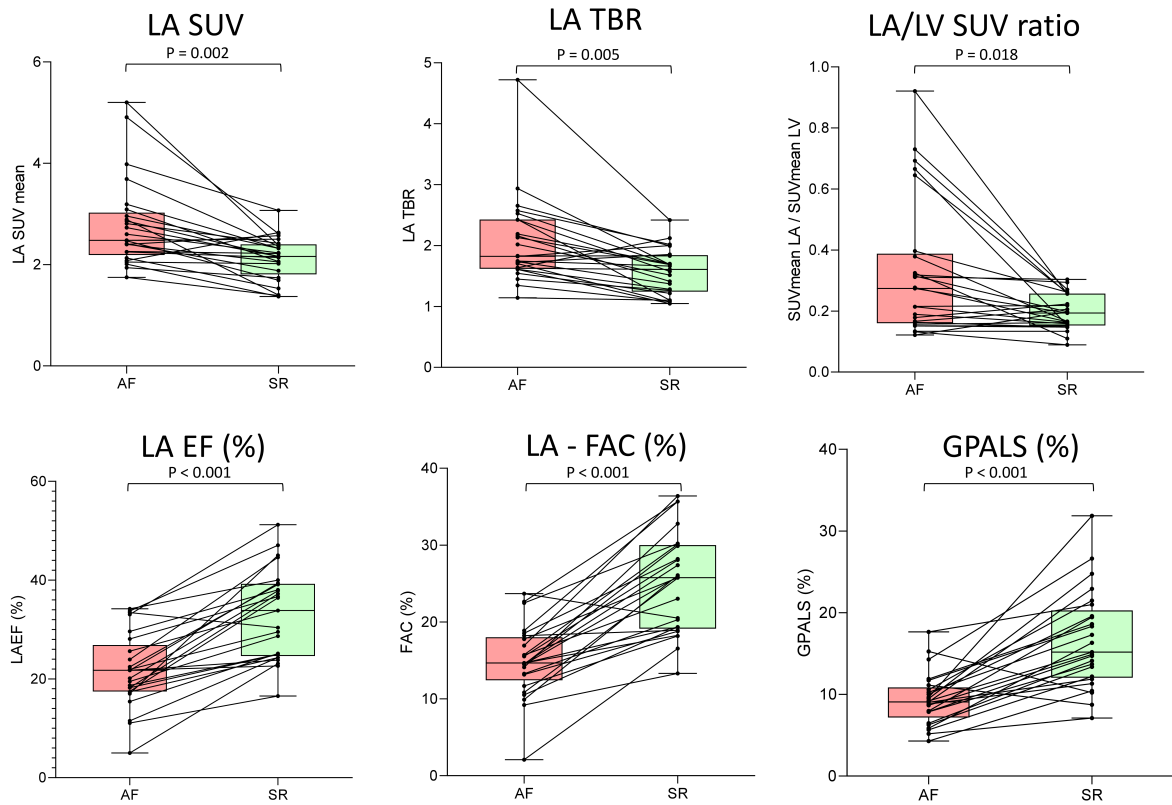


Figure 3: Individual evolution of LA FDG uptake and atrial contractile function between persistent atrial fibrillation and after sinus rhythm restore.

Spaghetti plot graph showing difference of LA FDG uptake (top panel) and atrial contractile function (bottom panel) between persistent atrial fibrillation (AF) and restoration of sinus rhythm (SR). Lines connect symbols for each subject and represent individual variation of FDG uptake or echocardiographic parameters. The box represents interquartile range, the line within the box indicates the median value, whiskers show minimum/maximum values. LA: Left Atrium; LV, left ventricle; SUV, Standardised Uptake Value; TBR, Target to Background Ratio; GPALS, Global Peak Atrial Longitudinal Strain; LAEF, Left Atrial Ejection Fraction and FAC, Fractional Area Change. * represent $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

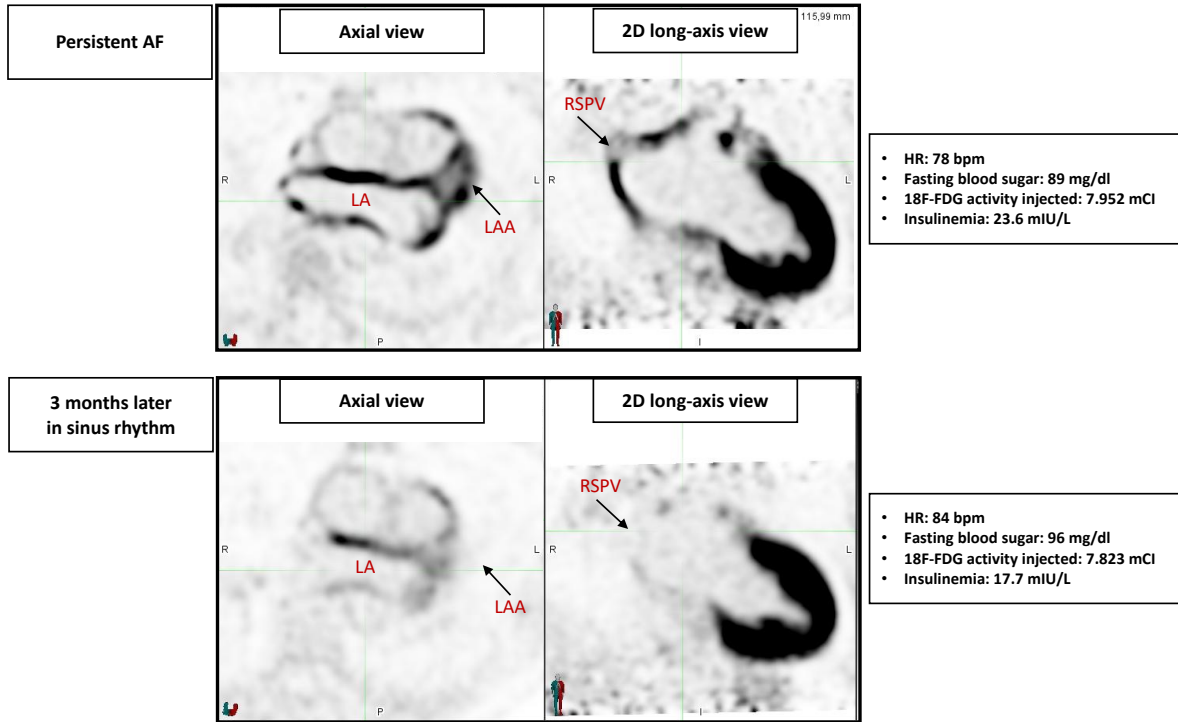


Figure 4: Example illustrating the reduction of atrial 18F-FDG uptake in patient during persistent AF and 3 months after sinus rhythm.

Patient preparation and metabolic conditions and image analysis and postprocessing were identical. LA: Left atrium, LV Left ventricle, LAA: Left atrial appendage, RSPV: Right Superior Pulmonary Vein.

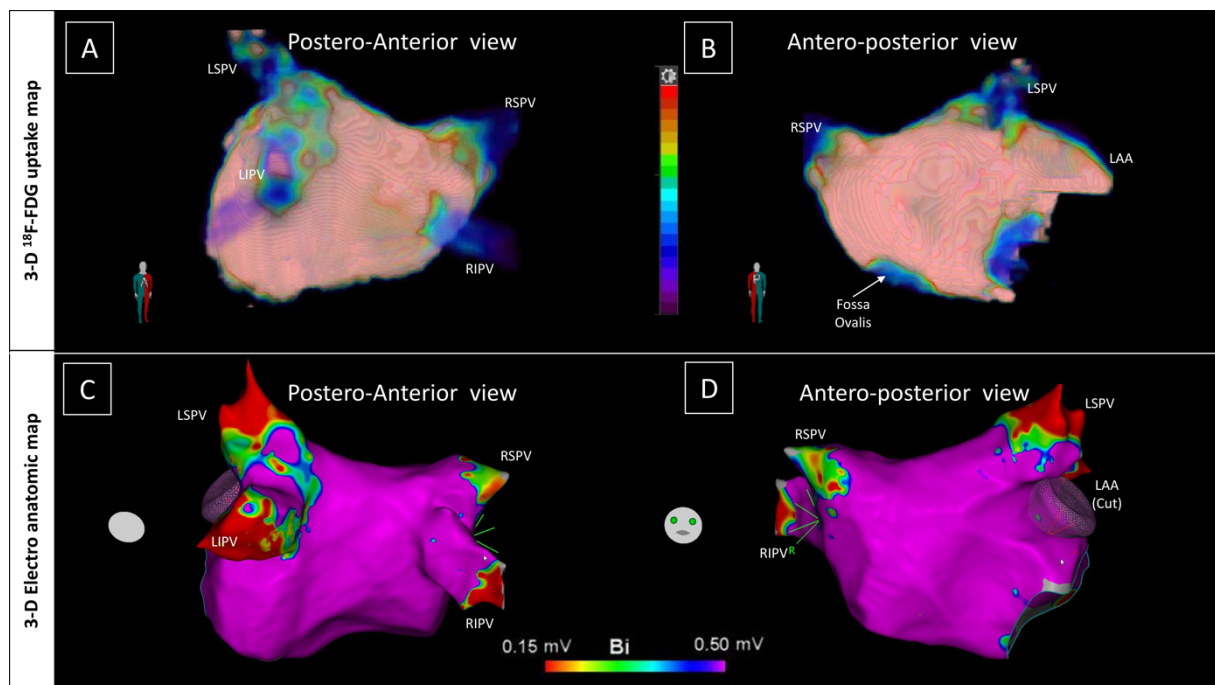


Figure 5: Example of a representative 3D ^{18}F -FDG uptake mapping in a patient without electrical LA remodeling: FDG-PET rendered LA model in posterior-anterior (A) and antero-posterior (B) views show homogeneous distribution of the tracer. Corresponding 3D electroanatomic maps during AF (C) and (D) shows electrically normal atrial tissue without low voltage area (purple color). LSPV: Left Superior Pulmonary Vein; LIPV: Left Inferior Pulmonary Vein; RSPV: Right Superior Pulmonary Vein; RIPV: Right Inferior Pulmonary Vein, LAA: Left Atrial Appendage.

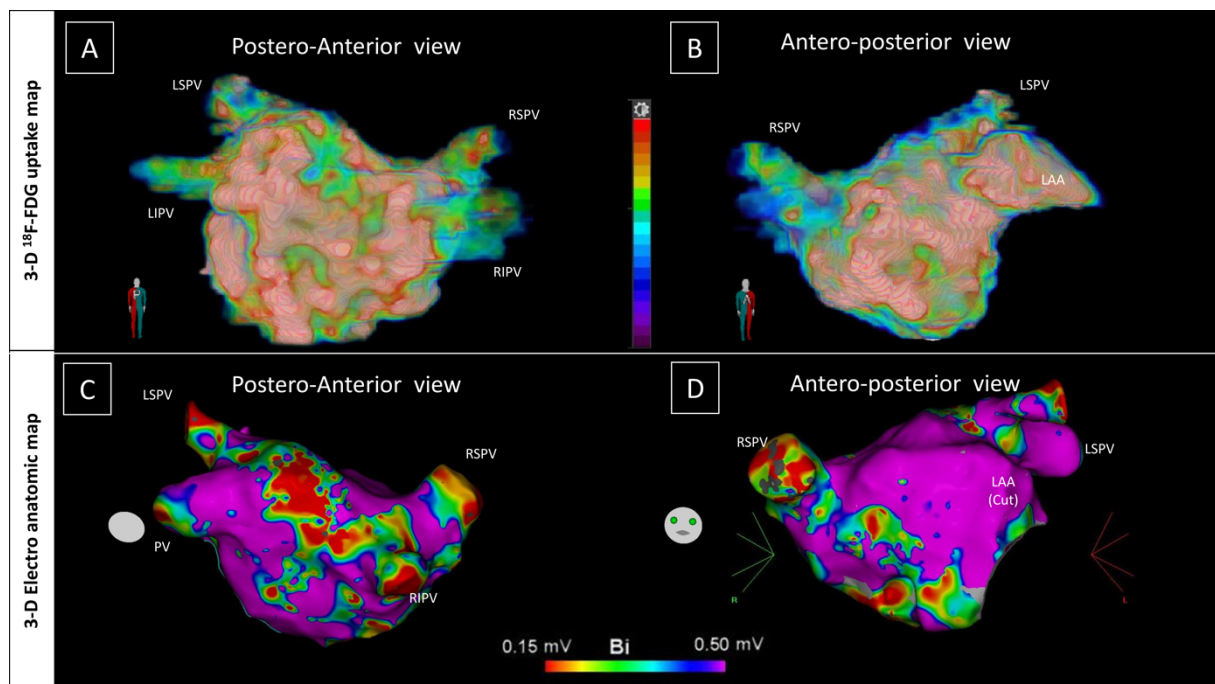
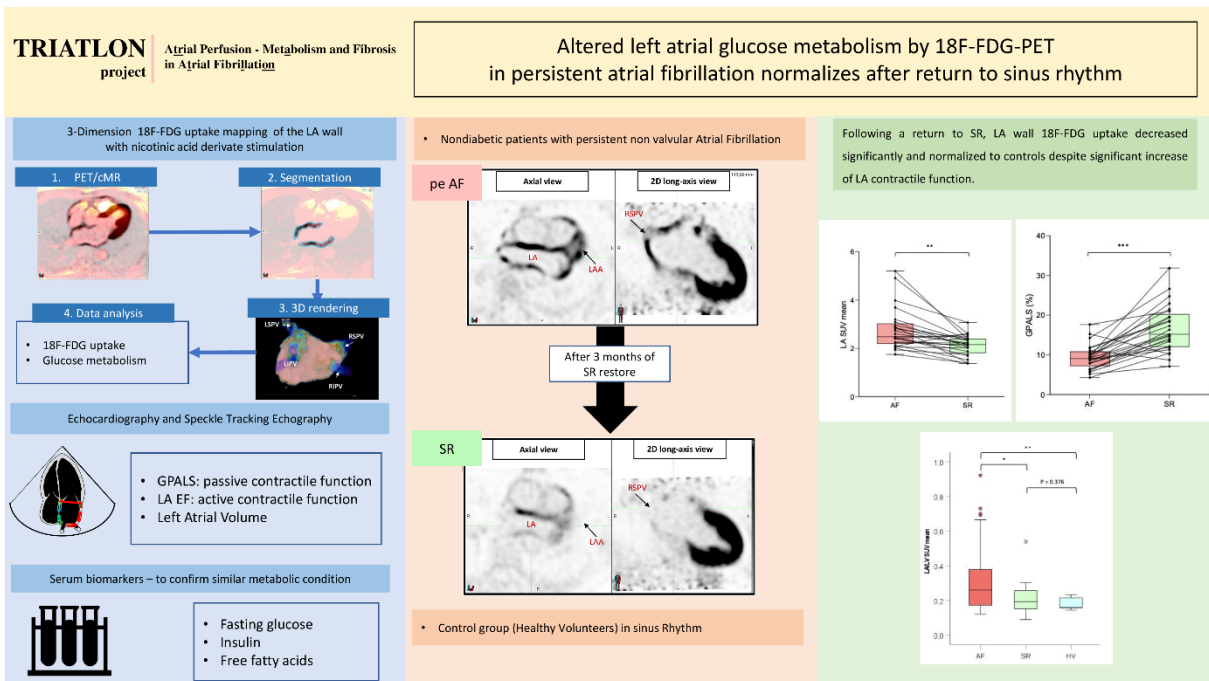


Figure 6: Example of a 3D ^{18}F -FDG uptake mapping example in a patient with LA electrical remodeling: FDG-PET rendered LA model in posterior-anterior (A) and antero-posterior (B) views show heterogeneous distribution of the tracer of the LA with low FDG uptake areas (green). Corresponding 3D electroanatomic maps (C) and (D) show low voltage area (green/red) in similar areas. LSPV: Left Superior Pulmonary Vein; LIPV: Left Inferior Pulmonary Vein; RSPV: Right Superior Pulmonary Vein; RIPV: Right Inferior Pulmonary Vein, LAA: Left Atrial Appendage.



- CHAPTER III - METHOD AND RESULTS -
ARTICLE 4

Article 4

Identification of left atrial structural remodeling and prediction of catheter ablation outcomes by low glucose uptake areas using nicotinic acid enhanced 18F-FDG PET/CT in persistent atrial fibrillation: a multimodal comparison.

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Abstract:

Background: Left atrial structural remodeling contribute to persistence of atrial fibrillation (AF), and impact catheter ablation (CA) outcomes.

Objective: To evaluate the utility of nicotinic acid stimulated ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) in identifying regions with low atrial glucose uptake (LGU) as a prospective indicator of atrial fibrosis, and to investigate its predictive value for CA outcomes in patients with persistent (pe)AF.

Material and Methods: 36 non-diabetic patients with peAF scheduled to undergo CA prospectively underwent nicotinic acid stimulated ^{18}F -FDG PET to evaluate the extent of atrial LGU, prior to CA. LGU was compared to low voltage area (LVA) by electroanatomical voltage mapping and late gadolinium enhancement (LGE) cardiac magnetic resonance (cMR) imaging as reference for atrial fibrosis. After CA, patients were followed up to 24 months to monitor AF recurrence.

Results: LGU correlated highly ($R^2=0.54$, $p<0.001$) with LVA extent, and significantly with left atrial volume index ($R^2=0.20$, $p=0.039$) and was among all parameters the best independent parameter to predict LVA with AUC 0.78; 95% CI:0.58-0.97. During follow-up, arrhythmia recurred in 18 (50%) of patients. Kaplan Meyer survival analysis showed that LGU extent $>17\%$, but not LGE-cMR predicted AF recurrence ($p=0.026$) with high accuracy (AUC 0.67; 95% CI:0.48-0.86)

Conclusion: LGU by nicotinic acid enhanced ^{18}F -FDG-PET precisely indicated LVA, suggesting fibrosis and its extent independently allowed to predict CA procedure success in patients with peAF. This suggest that FDG-LGU might be a valuable tool for non-invasive exploration of fibrosis and remodeling in atrial cardiomyopathy.

Keywords

Persistent Atrial Fibrillation, Glucose Metabolism, ^{18}F -FDG-PET, Left Atrial Structural Remodeling, Low Glucose Uptake extent.

Abbreviations and Acronyms

AF: Atrial Fibrillation

CA: Catheter Ablation

cMR: Cardiac Magnetic Resonance imaging

EF: Ejection Fraction

EAVM: ElectroAnatomical Voltage Mapping

FAC: Fractional Area Change

¹⁸F-FDG: ¹⁸F-FluoroDeoxyGlucose

GPALS: Global Peak Atrial Longitudinal Strain

LA: Left Atrium

LAA: Left Atrial Appendage

LAVI: Left Atrial Volume Indexed

LV: Left Ventricle

LVA: Low Voltage Area

LGE: Late Gadolinium Enhancement

LGU: Low Glucose Uptake

MRA: Magnetic Resonance contrast-enhanced Angiographic

Pe AF: Persistent Atrial Fibrillation

PET: Positron Emission Tomography

STE: Speckle Tracking Echography

SR: Sinus Rhythm

SUV: Standardized Uptake Value

TTE: Trans-Thoracic Echocardiography

V_{GLA}: global left atrial voltage

Introduction

Catheter ablation (CA) with pulmonary vein isolation (PVI) has gained widespread acceptance as the fundamental therapeutic approach for symptomatic paroxysmal atrial fibrillation (AF) (1-3). However, the management of persistent (pe) or long-standing persistent AF presents a more intricate challenge, marked by less favorable outcomes and a heightened recurrence rate following isolated PVI (4,5). Consequently, efforts persist to develop supplementary strategies aimed at enhancing the efficacy of AF ablation.

Left atrial (LA) structural remodeling is a hallmark of atrial cardiomyopathy in peAF, which is intricately linked to increased fibrosis, thereby prognosticating poorer outcomes (6-8). Therefore, in patients with peAF and LA cardiomyopathy, the identification and assessment of the AF substrate and specifically atrial fibrosis have high clinical value, as the CA strategy is progressively transitioning toward a customized approach, targeting these fibrotic areas as the underlying substrate for arrhythmia (9-12). The low voltage area (LVA), as assessed through electroanatomical voltage mapping (EAVM), has emerged as the gold standard for identifying such atrial fibrosis and guiding ablation strategies (9-11). However, due to its invasive nature, this procedure can only be conducted at the time of CA. Therefore, there is a growing interest in non-invasive cardiac imaging techniques such as trans-thoracic echocardiography (TTE) (13,14), and 3D gated late gadolinium-enhanced whole-heart navigator cardiac magnetic resonance (LGE-cMR) for identifying atrial fibrosis (15,16) and predicting CA success rate. (17). Nevertheless, ambiguous results have been reported when comparing LGE-cMR and EAVM in localizing LA fibrosis and the recent DECAAF II trial did not meet expectations with no demonstrable improvement in outcomes for cMR-guided ablation, confirming the difficulty in developing a tailored approach based on identifying the arrhythmic substrate with non-invasive imaging tools (18-20).

We recently presented findings indicating that nicotinic acid-stimulated ^{18}F -FDG uptake enables high-quality imaging of atrial metabolism in peAF (21). Building upon this, we hypothesize that akin to the left ventricle, under such metabolic conditions, atrial myocardial FDG uptake identifies the viability of atrial myocytes. Consequently, regions exhibiting metabolic defects and low atrial glucose uptake (LGU) could identify the absence of atrial myocardial viability and the presence of atrial fibrosis.

Hence, the current study aims to assess the potential usefulness of ^{18}F -FDG PET to identify LA fibrosis in peAF. To achieve this, we conducted a comprehensive multimodal comparison of FDG-PET LGU with other established markers of atrial scar, specifically LVA extent assessed by EAVM in patients with peAF undergoing CA. In addition, we sought to investigate whether LGU ^{18}F -FDG uptake could also serve predict the success of the CA procedures in these patients.

Methods

Detailed methods are provided in the supplementary appendix 1.

Study design and population

This single center study was approved by our institutional review board (IRB; 2018/17OCT/389. TRIATLON; Eudract reference 2019-001813-17A), and all participants provided written informed consent. The study protocols and methods were reported before (21). Briefly, adult patients referred to our facility for an initial CA procedure between January 2020 and September 2022 were eligible for inclusion, if they presented peAF, without history of prior AF ablation treatment. Exclusion criteria were: diabetes mellitus; hyperthyroidism; renal failure (glomerular filtration rate < 30 ml/m²); infiltrative, hypertrophic or other cardiomyopathies; severe valvular disease; and pre-operative transesophageal echocardiography-determined left atrial appendage (LAA) thrombus. The study protocol consisted of atrial cardiac magnetic resonance imaging, TTE and a nicotinic acid enhanced atrial ¹⁸F-FDG PET scan prior to EAVM and CA procedure. All imaging was performed while patients were in AF.

Cardiac MR

CMR was acquired using a 3T system and consisted of a 3D contrast-enhanced angiographic image (MRA) of the LA acquired after 0.1 mmol/kg Gd-DTPA injection, cine short-axis and long axis to evaluate left (LV) and right ventricular (RV) and LA end-diastolic and end-systolic volumes and ejection fractions (EF). Twenty minutes after contrast injection, evaluation of LA fibrosis was performed using a free-breathing navigator gated 3D whole heart late gadolinium sequence with a high resolution (1.5x1.5x1.5 mm).

Echocardiography

Pre-intervention, a comprehensive two-dimensional (2D) TTE was acquired to measure LV volumes, EF, diastolic function (mitral E/e' ratio), LA Volumes Indexed to body surface area (LAVI) and LAEF according to guidelines. Reservoir global peak atrial longitudinal strain (GPLAS) was computed using LV end-diastole as a zero-strain point. The LA stiffness index was calculated as E/e' divided by GPLAS (14).

Atrial ^{18}F -FDG PET imaging

^{18}F -FDG PET/CT was performed after overnight fasting and administration of a nicotinic acid derivative (Acipimox 250 mg) to maximize myocardial glucose uptake as described previously (21). A 10-minute partial volume and spillover corrected atrial image was acquired 90 minutes after injection of 300 MBq of ^{18}F -FDG. Atrial glucose standardized uptake value (SUV) was computed for each voxel by taking account for the injected ^{18}F tracer activity per patient body weight (MBq/kg) and decay correction.

Electroanatomical mapping and catheter ablation procedure

LA endocardial EAVM was performed with CARTO3 system at the time of CA. Bipolar peak-to-peak voltage amplitudes were recorded during AF then during right atrial (RA) pacing at 100 beats per minute (b.p.m) after electrical cardioversion. After voltage mapping, all patients benefited from point-by-point radiofrequency energy in an antral circumferential ablation pattern around each pulmonary vein pair according to the CLOSE protocol (22) with complete PVI and supplementary line ablation at the physician's discretion.

Image Processing and Fibrosis Quantification:

DICOM PET-CT, LGE-CMR and raw 3D data of the atria from the CARTO3 system were imported into Slicer-3D software. Point cloud measurements of bipolar voltages were orthogonally projected and interpolated on the model's surfaces to recreate 3D voltage maps. (Figure 1). Then PET-CT, LGE-cMR, and EAVM were visually aligned with MRA images, and the LA wall was segmented by delineating the epicardial and endocardial contours of the atria on axial slices. Later, 3D models of maximum intensity projection of PET-CT SUV values and LGE-CMR signal intensity in the LA wall were generated. Lastly, PET-CT, LGE-cMR, and EAVM models were co-registered with the MRA model, using an iterative closest point algorithm (12 degrees of freedom, allowing for deformation and scaling). Before quantification, we manually excluded pulmonary veins (PV) and the mitral valve using the dynamic modeler tool within Slicer3D. (Figure 1). LVA were identified when bipolar peak-to-peak voltage amplitudes were less than 0.30 mV during AF and 0.50 mV during RA pacing. The total LVA extent was calculated as the percentage of LA surface as previously described (21), and patients were separated into 2 groups of LVA extent: LVA-Group I with absence or low LVA extent (LVA extent $\leq 15\%$), LVA-

Group II with moderate or extensive LVA extent (LVA extent > 15%). The global left atrial voltage (V_{GLA}) was calculated as the mean of the bipolar peak-to-peak voltage amplitudes measured in the whole atria excluding the pulmonary veins and the mitral valve. Fibrosis by LGE-cMR was evaluated using as reference 2 standard deviations (SD) above the average intensity of the enhancement of the mean blood signal intensity. AF-LGE was classified by Utah stages as I to IV as, respectively, atrial LGE of 0% to 10%, 10% to 20%, 20% to 40%, and >40% LGE. (17) Finally, the LGU region was defined as the LA surface exhibiting less than mean + 5SD of the blood signal SUV.

Statistical analysis.

$P < 0.05$ was considered indicative of a statistically significant difference. Continuous values were assessed for normality and expressed as the mean $\pm$ one SD or the median with interquartile range (IQR) depending on their distribution. Categorical variables were expressed as counts and percentages. To compare groups, Student's t-test and chi-square tests were used as appropriate. Analysis of variance was used to normalize for confounding variables. Multivariable linear regression models were used to compare patient and imaging modalities characteristics with severity of LVA extent parameters. ROC models and Logistic regression models were used to compare several thresholds with continuous variables. Area under the curve (AUC) were compared with Delong test. The relationship between the different imaging modalities were evaluated through linear regression analysis and the Pearson correlation coefficient. ROC models and Logistic regression models were used to predict LVA extent. Patients were separated into 2 groups according to the median LGU extent value (LGU-Group I with $LGU \leq$ median value and LGU-Group II with $LGU >$ median value). Survival free from atrial fibrillation recurrence after CA were analyzed using Kaplan-Meier and multivariate Cox survival analysis.

Results

Patient characteristics

Patient baseline characteristics are summarized in **Table 1**. Thirty-eight patients with peAF and five healthy volunteers were enrolled in the study. Two peAF patients were excluded, one due to the inability to obtain images caused by PET scanner failure and the other due to poor image quality resulting from an issue with tracer injection. No statistically significant differences were observed in terms of sex, age, and weight between AF patients and healthy volunteers. However, patients exhibited a tendency for higher body mass index (BMI) than controls, along with a significantly higher prevalence of cardiovascular risk factors such as hypertension and smoking. At the time of the study, there were no significant differences in systolic blood pressure, estimated Glomerular Filtration Rate (eGFR), glycemia, insulinemia, and free fatty acid levels between patients and controls. The heart rate was slightly but significantly higher in patients than in controls.

In the patient group, AF persisted for more than six months in 19 (53%) individuals, with a median duration of persistent AF being 150 days [120-261]. The median CHA2DS2-VASc score was 2 [1-3], and four (11%) patients had a history of stroke or systemic thromboembolism. Echocardiographic measurements, including E/e', and LVEF, were similar between patients and controls, while LAVI, LA diameter and LA stiffness were lower in controls. CMR left and right ventricular volumes and ejection fractions were similar. None of the controls exhibited LGE in the myocardium (LGE fibrosis: 0% [0;2.3]), and no patients showed any indications of infiltrative diseases such as amyloidosis or sarcoidosis.

The average atrial LGE extent in peAF patients was 12.28±9.47% (range 1-45%). Among the patients, nine (25%) were classified as Utah stage I, 20 (56%) as Utah stage II, six (19%) as Utah stage 3, and only one as Utah stage 4. Healthy volunteers had a trivial LGU extent, with a median of 2.7% [2.5;4.2]. In contrast, peAF patients exhibited variable LGU extent, with a median of 16.8% [7.6;42.6]. Based on median LGU extent, patients were categorized into two groups: Group I (LGU ≤17%, median 7.6% [3.7;10.2]) and Group II (LGU extent >17%, median of 44.5% [24.9;56.6]) (P<0.001). Patients in LGU Group II, compared to Group I, had a similar age but more frequently presented with hypertension (P=0.041) and hypercholesterolemia (P=0.046). They also had a longer median duration of persistent AF, slightly lower LVEF, GPALS,

and higher LA diameter or LA stiffness index. LGE fibrosis and LVEF by CMR were similar, but 3D LAVI was non significantly larger ($P=0.133$) in patients with high LGU extent.

Procedural and EAVM characteristics

The procedural characteristics are summarized in Table 2.

EAVM were successfully generated during AF in all patients before CA procedure, utilizing 2072 ± 874 acquired points and revealing a median LVA extent of 9.75% [3.07;19.4] and median V_{GLA} of 0.68 mV [0.55;1.01]. EAVM data acquired during RA pacing are detailed in supplementary appendix 2. A majority of patients, 31 (86%), presented with LVA. Within this cohort, 23 (64%) exhibited LVA extent below 15%, with an average LVA extent of $5.25\% \pm 4.67$, while 13 (36%) demonstrated LVA extent exceeding 15%, with an average LVA extent of $27.59\% \pm 10.03$ ($P<0.001$). Notably, LVA extent was found to be higher and V_{GLA} to be lower in patients with elevated levels of LGU ($P<0.001$ and $P=0.002$ respectively). PVI was successfully executed in all patients with no discernible variation in the ablation strategy, encompassing box isolation, other lines, and complex fractionated atrial electrograms (CAFE), between patients with low or extensive LGU. Importantly, no complications such as cardiac perforation, systemic embolism or stroke, atrial-esophageal fistula, pulmonary stenosis, or mortality were encountered during the procedure.

Correlations between LVA extent and LGU extent, LGE extent and LAVI.

Figure 2 depicts 3 examples of co-registered segmented 3D ^{18}F -FDG LGU maps with 3D EAVM LVA acquired during AF. In Figure 2A, a patient is illustrated without detectable LGU area and no LVA extent. Figure 2B displays a patient with a mild LGU extent (accompanied by corresponding LVA) in the posterior and inferior regions of the left atrium around the ostia of the left inferior PV and right inferior PV, as well as in the anteroseptal part of the LA. Figure 2C presents an instance of extensive LGU and LVA, where the tracer distribution's heterogeneity is more pronounced. Significant LGU extent is observed in the LA's posterior and inferior parts, along with the anterior and anteroseptal parts, corresponding to abnormal atrial tissue with LVA in the equivalent regions. Quantitative analysis of this relationship confirmed a good correlation of $R^2=0.54$ ($P<0.001$) between LGU and LVA extent. (Figure 3A). The relationship between EAVM parameters and PET parameters is also illustrated by a good

correlation between V_{GLA} and LA mean SUV ($R^2=0.42$; $p<0.001$). (Figure 3B) Atrial fibrosis evaluated with LGE cMR did not correlate with either the extent of low voltage areas ($P=0.62$, $R^2 = 0.01$) (Figure 3D) nor with LGU ($P = 0.52$, $R^2 = 0.01$) (Figure 3F). Finally, LAVI correlated significantly but weakly with LVA extent ($P=0.039$, $R^2 = 0.20$). (Figure 3C).

The ROC curves for the prediction of moderate or important LVA extent during the ablation procedure for the different noninvasive imaging parameters are shown in Figure 4. LGU had the highest area under the curve (0.78; 95% CI:0.58-0.97) for prediction of LVA extent during AF, which was significantly higher than the AUC for LGE extent fibrosis (AUC=0.55; 95%: 0.32-0.79) ($P=0.03$). LAVI presented a good value to predict LVA extension (AUC=0.63; 95% CI:0.43-0.83). Predictors of LVA extent are shown in Table 3. Univariate predictors of LVA were LAVI, E/e' , LA stiffness, LGU extent and LA SUV. In a multivariate linear regression model, LGU was the best independent predictor of LVA extent ($P<0.001$). Results were similar during RA pacing (supplementary appendix 2).

Follow-up and AF recurrence outcome

After the CA procedure, 25 patients (69%) were treated with beta-blockers, 4 patients (11%) with sotalolol, 6 patients (17%) with amiodarone, and 6 patients (17%) with class I antiarrhythmic drugs. A documented recurrence of AF lasting longer than 30 seconds after the initial ablation procedure, with or without the use of antiarrhythmic medications, occurred in 18 patients (50%). Patients with recurrent atrial tachyarrhythmias were older (66.5 ± 8.7 vs 62.4 ± 8.3 years, $P=0.090$), more often hypertensive (46.7% vs. 31.6%, $P=0.195$), and had a higher CHA_2DS_2 -VASc score but, none of the clinical parameters or antiarrhythmic drug treatment administered after CA procedure showed a statistically significant difference between patients with and without AF recurrence. Clinical parameters and noninvasive imaging modalities predictors of arrhythmia recurrence are shown in Table 4. Univariate predictors of AF recurrence were LAVI and LGU extent greater than 17 %. In multivariate regression analysis, high LGU extent remained the only independent predictors of recurrent atrial tachyarrhythmias following CA procedures ($P<0.001$). The ROC curves for the prediction of AF recurrence after the CA procedure for the different imaging parameters are shown in Figure 5, and Kaplan–Meier curves for estimation of freedom from documented atrial fibrillation according to the 2 LGU extent groups are shown in Figure 6. LVA extent had the highest AUC (0.74; 95% CI:0.56-0.92) to predict AF recurrence, which was higher than LGE

(AUC 0.55; 95% CI:0.33-0.76). V_{GLA} had also a good predictive value with AUC= 0.67 (95% CI:0.48-0.87). Among the noninvasive imaging tools, LAVI and LGU extent had the best predictive accuracy to predict AF recurrence (AUC = 0.71; 95% CI:0.53-0.89 and 0.67; 95% CI:0.48-0.86, respectively). AF recurrence-free survival rates with or without the use of antiarrhythmic medications were respectively 77% in patients with low LGU extent and 35 % in patients with moderate or extensive LGU extent (log-rank, $P=0.026$).

Discussion

The principal findings of our present study can be summarized as follows:

1. A three-dimensional quantitative map of LGU extent with ^{18}F -FDG PET showed a good correlation with LVA extent.
2. Among the non-invasive modalities, LGU evaluated with ^{18}F -FDG PET in the atrial walls had the highest diagnostic accuracy for predicting LVA extent.
3. LGU extent quantification with 3D ^{18}F -FDG PET map independently allowed to predict the success of CA procedure in persistent AF patient.

PVI is now widely accepted as the cornerstone of AF ablation and is recommended during all CA procedures (1-3). Nevertheless, the notable recurrence rates observed in patients with persistent and long-standing persistent AF following PVI alone have prompted ongoing efforts to identify supplementary strategies aimed at enhancing the outcomes of AF ablation (4,5). Therefore, in patients with peAF, the identification and the assessment of the LA cardiomyopathy substrate have gained clinical significance. The evolving trend in ablation strategy is increasingly tailored, relying on the treatment of fibrotic areas discerned through various imaging technologies to ameliorate the underlying substrate of arrhythmia. (9-12)

In our study we used 3D EAVM combining anatomical and electrical information by catheter sequential point-by-point or simultaneous multielectrode mapping, as reference standard to identify atrial fibrosis. Indeed, EAVM facilitates the identification of LVA, voltage reduction, slowed conduction, and complex fractionated signals—manifestations indicative of structural changes and the hallmark of fibrosis (23). Studies have shown that patients with peAF have a higher extent of LVAs than those with paroxysmal AF. Notably, the extent of LVAs has been identified as an independent predictor for recurrence events following AF ablation

procedures. (24) Furthermore, these LVAs can be directly targeted with radiofrequency ablation to perform substrate modification. These tailored and therapeutic approaches targeting atrial fibrosis have been reported to improve ablation success rates in persistent AF patients. (9-11). However, EAVM with LVA is an invasive method only available at the time of ablation and is not of value for selecting catheter ablation candidates prior to the procedures. In the present study we conducted a comprehensive comparison between EAVM parameters and LGE-cMR, along with echocardiographic parameters assessing structural remodeling and PET parameters. As previously described, LA size by echocardiography emerged as a pertinent factor associated with the procedural outcome of AF and demonstrates correlation with atrial fibrosis. (2,14) However, its utility is constrained by low sensitivity, as it may overlook small amounts of fibrosis. Our study unveiled a significant albeit modest correlation between LAVI and LVA extent, a moderate correlation with LGU, and a stronger predictive association with the success rate of the procedure. Remarkably, the majority of echocardiographic parameters linked to atrial remodeling exhibited significantly elevated values in the cohort of patients displaying a considerable extent of LGU. This underscores the relevance of incorporating additional echocardiographic parameters such as LAVI obtained through three-dimensional transthoracic echocardiography (3D TTE), as well as metrics assessing atrial stiffness, LA asynchrony, and LA contractile dysfunction through speckle tracking echocardiography and longitudinal strain. These parameters provide valuable insights into the evaluation of LA structural remodeling and atrial cardiomyopathy. (14)

We also performed a comprehensive cross-comparison of ^{18}F -FDG LGU and LVA to cMR- LGE which has been advocated as a non-invasive imaging method for identifying atrial fibrosis. (16). The DECAAF study proposed a scoring system (Utah score) for the area of delayed enhancement, the extent of fibrosis evaluated by LGE cMR predicting the outcome of AF ablation and suggesting that cMR quantification of fibrosis may play a role in the appropriate selection of patients most likely to benefit from AF ablation (17). Some studies have shown a good correlation between LGE-cMR and LVA extent with EAVM. (16,17). In our present works, however, LGU did not correlate well LGE cMR, but LGE-cMR did also not correlate well to LVA-EAVM nor predict outcomes. This is accordance with other works which found disappointing correspondence between LGE-cMR and EAVM (18,19). Potential explications may be the difficulties of the acquisition process, particularly during arrhythmia, (18,19), and the variability in specialized post-imaging processing and threshold to differentiate normal from

fibrotic tissue among different studies (25-28). In our study we used an identical protocol as the DECAAF study and tested several reported methods for LGE quantification, however, did not find superior results with any method, as detailed in supplementary appendix 3. Finally, the value of LGE-cMR has recently been questioned by the negative results of the DECAAF II trial which could not find added value in AF recurrence with an LGE-cMR-guided ablation strategy (20).

The novelty of our study lies in proposing nicotinic acid stimulated ^{18}F -FDG PET to identify atrial fibrosis in atrial cardiomyopathy. Indeed, previous research has shown that atrial cardiomyocyte energy metabolism during AF leads to metabolic stress and is associated with a series of modifications at the cellular level, including a metabolic shift to a more fetal phenotype and AMP-activated protein kinase activation. (8, 29) These changes increase glucose transporters' expression and promote its trafficking into the sarcolemma, increasing glucose uptake. (8) Moreover, several retrospective and prospective works, including paroxysmal and peAF patients, have studied FDG uptake in LA using strategies (prolonged fasting, dietary manipulation, or heparin loading) to suppress physiological myocardial FDG uptake. These studies proposed that the FDG uptake was related to the increased activity of atrial structures and epicardial adipose tissue and inversely correlated with LA fibrosis. (30-32) However, the image quality of FDG PET in the LA was poor due to variable uptake and partial volume effect and thin atrial wall. Also, under such conditions FDG signal may corresponded to the metabolic activity of either the atrial wall, the epicardial adipose tissue, or both. (31) In the TRIATLON project, the study population was homogenous with non-diabetic pe AF patients. We demonstrated that after administration of a nicotinic acid derivative (Acipimox), the LA behaves similar to the LV enhancing significantly atrial ^{18}F -FDG uptake during AF (21,33). Also, we optimized acquisition for the LA, enabling excellent visualization of the LA, with sufficient spatial resolution to visualize and analyze various structures, including the fossa ovalis, mitral annulus, pulmonary vein ostia, and LAA and allowing creation of a 3D LA uptake map, provides a faithful representation of the LA wall anatomy (21,33). In the present study we showed that LA mean SUV correlated with V_{GLA} and that FDG uptake defects in the LA map closely correspond to LVA on EAVM, suggesting that these LGU areas represent LA fibrosis. We also showed that areas of LGU predict success of CA, further supporting the value of the technique to non-invasively evaluate structural remodeling.

Clinical Implications

The present study demonstrated the ability of acipimox enhanced ^{18}F -FDG PET to accurately identify LVA and structural remodeling of the LA in patients with peAF and suggests that this technique might be useful for predicting outcomes of CA. Indeed FDG-PET performed better than LGE-cMR, which suffered from poor image quality and was not accurate to identify LVA. Nicotinic acid enhanced ^{18}F -FDG-PET could thus be a better alternative to LGE-CMR for preoperative assessment of fibrosis prior to CA in peAF, although the technique has some disadvantages, in particular high cost, and radiation exposure. Nevertheless, if PET cMR allows better identification of CA candidates, these limitations are clearly better than performing CA.

Limitation

This study was conducted at a single center and featured a limited sample size. The clinical insights gained from our investigation warrant validation in larger patient cohorts. Notably, diabetes was an exclusion criterion in our study due to potential interference with FDG uptake. Future studies should explore the utility of PET in patients with diabetes to visualize FDG uptake. It is essential to acknowledge that FDG PET may not exclusively evaluate atrial metabolism; it could also reflect the metabolism of epicardial adipose tissue or inflammatory macrophages. AF induces a hibernating-like phenotype in atrial cardiomyocytes, leading to fibroblast replacement and the development of fibrotic tissues. While obtaining LA biopsies is imperative to address these complexities, our study's positive correlation between the three-dimensional quantitative analysis of LGU with the ^{18}F -FDG uptake map and the extent of LVA aligns with previous observations (21, 33), indicating that LGU could be associated with atrial electrical scarring in whom fibroblast replaced cardiomyocyte and could predict ablation procedure outcome. Finally, LVA measurements were acquired with CARTO3 and a deflectable 12-pole circular mapping catheter with 25-15 loop diameter, and 8mm inter-electrode spacing. Therefore, our findings might not apply to other mapping systems and catheters.

Conclusions

Low glucose uptake areas on nicotinic acid enhanced ^{18}F -FDG PET in patients with peAF closely correlated with areas of electrical low voltage area during electroanatomic voltage mapping indicating that LGU detects left atrial fibrosis. Furthermore, the spatial extent of LGU predicted the success after CA procedure indicating that this parameter can non-invasively evaluate the severity of atrial structural remodelling in atrial cardiomyopathy. These findings support the potential role of ^{18}F -FDG-PET in improving the evaluation and management of patients with peAF candidates for CA procedures.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1 Characteristics of the study population

	All Patients	LGU≤17%	LGU>17%	P-value*
Clinical Parameters				
Age (years)	64.3±8.7	62.9±8.4	65.5±8.8	0.205
Sex (male)	27 (75)	14 (77.7)	13(72.2)	0.341
Persistent AF duration (days)	200 [180;285]	109 [105;190]	180[150;365]	0.056
eGFR (ml/min)	74±22	73±12	69±23	0.285
CHA ₂ DSVAS ₂ C	2 [1;3]	2 [1;3]	2 [1;3]	0.5
CHARGE-AF	12.4±1.1	11.8±0.9	12.6±1.2	0.106
Antiarrhythmic drugs	16 (44.4)	9 (50)	7 (38.8)	
Cardiovascular risk factors				
Active tabaco use	11 (30.5)	6 (33.3)	5 (27.8)	0.362
CAD	7 (18.42)	2 (11.1)	5 (27.8)	0.108
Hypertension	14 (36.8)	4 (22.2)	9 (50)	0.041
Hypercholesterolemia	16 (42.1)	6 (33.3)	11 (61.1)	0.046
Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	NA
Echocardiographic parameters				
LVEF (%)	58.2±9.4	61.4±7.7	55.2±10.1	0.029
LAVI (ml/m ²)	59.9±18.3	57.0±19.6	62.9±16.9	0.178
E/e'	8.8±3.9	7.3±2.1	10.2±4.6	0.15
LA diameter (mm)	47.2±5.21	45.6±5.2	48.7±4.9	0.044
LA stiffness index	1.2±0.8	0.9±0.3	1.4±0.9	0.014
GPALS (%)	9.0±3.4	9.5±3.8	8.6±3.1	0.213
PET parameters				
LA mean SUV	3.6 [3.2;4.7]	4.7 [4.3;5.9]	3.2 [2.9;3.6]	< 0.001
LA LGU (%)	16.8 [7.6;42.6]	7.6[3.7;10.2]	44.5[24.9;56.6]	< 0.001
CMR parameters				
LVmass indexed (g/m ²)	55.4±13.2	53.9±17.2	62.2±20.8	0.097
LVEDVi (ml/m ²)	77.5±20.16	77.9±17.7	80.8±22.3	0.339
LVEF (%)	50.1±8.4	52.1±7.3	50.1±9.1	0.227
RVEDVi (ml/m ²)	75.5±15.2	76.6±14.8	74.2±14.1	0.307
RVEF (%)	51.1±8.2	51.4±7.1	52.1±9.1	0.371
LAVI (ml/m ²)	77.0±24.1	71.9±26.7	81.4±20.5	0.133
Fibrosis (%)	10.0 [5.6;17.0]	8.9[6.8;16.9]	11.5[4.7;15.3]	0.349

Table 1: Data are presented as mean±SD, number (percentage), or median [interquartile range]. AF: atrial fibrillation; BMI, body-mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; NA, not applicable; LVEF, left ventricular ejection fraction; LA, left atrium; LAVI, left atrium volume indexed; LV, left ventricle; GPALS, global peak atrial longitudinal strain; LV, left ventricle, LGU, low glucose uptake; SUV, standardized uptake value. LVEDVi, left ventricle end diastolic volume indexed; RVEDVi, right ventricle end diastolic volume indexed and RVEF, right ventricular ejection fraction. P-value* compare group LGU≤17% and LGU > 17%.

Table 2 Procedural characteristics

	All patients	LGU≤17%	LGU >17%	P value*
LVA extent (%)	9.8[3.1;19.4]	3.5[0.0;9.9]	19.3[7.3;31.5]	<0.001
V _{GLA} (mV)	0.68[0.55;1.01]	0.94[0.67;1.39]	0.58[0.42;0.68]	0.002
AF rhythm during EAVM	36(100)	18 (100)	18 (100)	NA
PVI	36(100)	18 (100)	18 (100)	NA
CTI	5(13.9)	3(16.6)	2(11.1)	0.685
Posterior wall isolation	6(16.6)	2(11.1)	4(22.2)	0.357
Mitral Isthmus	3(8.3)	1(5.5)	2(11.1)	0.534
CAFE	2(5.5)	1(5.5)	1(5.5)	0.971
Procedural time (min)	164±36	159±37	163±35	0.765
Irradiation (mGy/cm2)	2994±1519	2869±1242	3075±1661	0.665

Table 2: Data are presented as mean±SD, number (percentage) or median [interquartile range]. AF, atrial fibrillation; CAFE, complex atrial fractionated electrogram; CTI, cavo-tricuspid isthmus ablation; EAVM, electroanatomical voltage mapping; LVA, low-voltage area; V_{GLA}, global left atrial voltage; NA, not applicable; PVI, pulmonary vein isolation. P-value* compare group LGU≤17% and LGU > 17%.

Table 3: Multivariate linear model for the prediction of LVA.

	Univariate analysis		Multivariable model	
	Coefficient [95% CI]	P value	Coefficient [95% CI]	P value
Age (years)	0.39 [-0.18;0.92]	0.133		
eGFR (ml/min)	-0.14 [-0.39;0.09]	0.226		
CHA ₂ DSVAS ₂ C	0.42 [5.45;20.04]	0.789		
LAVI	0.20 [-0.04;0.45]	0.094	1.74 [-0.25;0.31]	0.092
E/e'	2.05 [1.08;3.03]	<0.001*	3.08 [0.42;2.01]	0.005*
LA stiffness	11.51 [6.78;16.27]	<0.001*		
LGU extent	0.41 [0.27;0.55]	<0.001*	4.46 [0.17;2.01]	<0.001*
LA SUV	-3.82 [-6.54;-1.10]	0.007*		
LGE Fibrosis	0.12 [-0.37;0.62]	0.623		

Table 3: Regression coefficients are presented as value [95% CI, confidence interval]. LVA, low voltage area. LA, left atrium. LAVI, left atrium volume indexed. SUV, standardized uptake value. LGU, low glucose uptake. eGFR, estimated glomerular filtration rate. LGE, late gadolinium enhancement. * indicate P value <0.01.

Table 4: Cox Uni and Multivariate predictors for prediction of recurrent arrhythmia

	Univariate analysis		Multivariable model	
	Coefficient [95% CI]	P value	Coefficient [95% CI]	P value
Age (years)	1.06 [0.97;1.16]	0.177		
eGFR (ml/min)	1.02 [0.97;1.06]	0.383		
CHA ₂ DSVAS ₂ C	1.48 [0.89;2.46]	0.136		
LAVI	1.05 [1.01;1.10]	0.044	1.05 [0.99;1.10]	0.067
E/e'	1.14 [0.91;1.42]	0.249		
LA stiffness	1.39 [0.53;3.62]	0.501		
LA SUV	0.81 [0.49;1.32]	0.385		
LGU extent	1.02 [0.99;1.05]	0.303		
LGU extent > 17%	5.96 [1.33;26.66]	0.020	5.72 [1.14;28.58]	0.034
LGE Fibrosis	1.01 [0.94;1.09]	0.719		

Table 4: Regression coefficients are presented as value [95% confidence interval]. LA, left atrium. LAVI, left atrium volume indexed. SUV, standardized uptake value. LGU, low glucose uptake. eGFR, estimated glomerular filtration rate. LGE, late gadolinium enhancement.

Supplementary appendix 1 - Detailed methods

Study design and population

This single center prospective trial was approved by our Institutional Review Board (IRB; 2018/17OCT/389-TRIATLON; Eudract reference 2019-001813-17A), and all participants provided written informed consent.

Inclusion and exclusion criteria were patients with persistent (pe) symptomatic atrial fibrillation (AF) referred to our facility for initial CA procedure between January 2020 and September 2022 met the inclusion criteria if they were non-diabetic, between the ages of 18 and 80, and had no history of prior AF ablation. The following conditions were excluded: hyperthyroidism; renal failure (glomerular filtration rate < 30 ml/m²); infiltrative, hypertrophic, or other cardiomyopathies; severe valvular disease; and pre-operative transesophageal echocardiography-determined left atrial appendage (LAA) thrombus. Before CA, the study protocol included cardiac magnetic resonance (cMR) imaging, trans-thoracic echocardiography (TTE) and an acipimox-enhanced atrial ¹⁸F-FDG PET scan in AF. A total of 43 subjects were included in the study, comprising 38 patients and five healthy, age-matched controls without history of atrial fibrillation or cardiac disease.

Cardiac Magnetic Resonance

CMR was acquired using a 3T system (Signa Premier, GE Healthcare). All patients were in AF during acquisition. After localizer a 3D contrast-enhanced angiographic image (MRA) of the left atrium was acquired after 0.1 mmol/kg Gd-DTPA injection. Then ten to twelve consecutive short-axis images, and one each of 2-, 3- and 4-chamber long-axis images were acquired using a retrospectively gated cine SSFP sequence (8 mm slice thickness, and 2 mm spacing, matrix 200x180, field of view 360 mm, 30 phases, flip angle 65 degrees) to allow for the evaluation of left ventricular (LV) and right ventricular (RV) myocardial end-diastolic (EDV) and end-systolic volumes (ESV), ejection fraction (EF), and mass. Thereafter a stack of consecutive short-axis late gadolinium (LGE) images and respectively and one each of 2-, 3- and 4-chamber long-axis images were acquired in the same orientation as cine images with a segmented gradient echo 2D phase sensitive inversion recovery sequence (slices thickness 8 mm, spacing 2 mm, matrix 200x180 mm, field of view 360 mm) in identical location as the cine images to evaluate focal myocardial fibrosis. Images were analyzed by one single reviewer using free-of-charge software segment version 3.1 (34). Finally, 20 minutes after contrast injection, atrial

fibrosis was evaluated by a 3D ECG-triggered, free-breathing navigator gated whole heart LGE sequence (Hearty, work in progress GE Medical images). Imaging parameters were Matrix 400x360 mm, 70-80 mm height with isotropic voxel acquisition (1.5x1.5x1.5 mm), flip angle 20 degrees, anterior-posterior frequency direction, Bandwidth 700 Hz, Repetition time 3.5 ms, Inversion time 260-300 ms, gating in atrial end diastole.

Echocardiography

Two-dimensional (2D) TTE was acquired while patients were in AF using EpiQ echocardiographic systems (Philips Healthcare, Andover, MA, United States) and stored digitally on a PACS system (Philips Intellispace). One observer (SMA) analyzed the images offline, and all measurements were performed by averaging two cardiac cycles. Left ventricular (LV) volumes and ejection fraction were calculated using Simpson's biplane method. The E/e' ratio was calculated by dividing the peak mitral flow E wave by the average of septal and lateral e' tissue Doppler velocities. LA volume analysis was performed on dedicated apical 4 and 2-chamber views of the LA acquired with a frame rate between 60 and 80 frames per second and analyzed using Image-ArenaTM cv4.6 (TomTec Imaging Systems, Unterschleissheim, Germany) in duplicate by two experienced blinded echocardiographers (SMA and QG). The LA endocardium was traced automatically with manual adjustment if needed. LA stiffness index was calculated as E/e' divided by reservoir global peak atrial longitudinal strain (GPALS). According to the EACVI/ASE Task Force's recommendation, GPALS was computed using LV end-diastole as a zero-strain point during AF. (14)–Maximal and minimal LA volume was measured at the end of LV systole and indexed to the body surface area (LAVI).

Atrial ¹⁸F-FDG PET imaging

The protocol for the PET imaging has been reported previously (21). ¹⁸F-FDG PET/CT was conducted utilizing a high-resolution digital 64-slice PET/CT system (Vereos TOF- Philips Healthcare, Cleveland, OH). Patients underwent testing after overnight fasting and received a nicotinic acid derivative (Acipimox 250 mg) to maximize myocardial glucose uptake. A 10-minute electrocardiogram (ECG) non-gated acquisition was acquired 90 minutes after 300 MBq of ¹⁸F-FDG was injected. Attenuation-corrected PET images (voxel size, 2 mm using standard manufacturer OSEM algorithms) were reconstructed from the CT data employing a 3D ordered-subset expectation maximization algorithm (15 subsets, 4 iterations). After

correcting for partial volume and spill-over effects, the atrial glucose standardized uptake value (SUV) was computed for each voxel as tracer activity (MBq/mL)/injected dose per patient body weight (MBq/kg) after decay correction.

Electroanatomical voltage mapping and catheter ablation procedure

The LA endocardial electroanatomical voltage mapping (EAVM) was captured using the ConfiDENSE™ CARTO3 system v6.0.70 along with the 2515 Variable Loop Lasso Multi-Electrode Eco Nav from Biosense Webster, Diamond Bar, CA and then using the ablation catheter (SmartTouch, Biosense Webster, Inc) to confirm low voltage area (LVA). Bipolar peak-to-peak voltage amplitudes were recorded during AF then during right atrial (RA) pacing at 100 beats per minute (b.p.m) after electrical cardioversion. Over 1000 measurements were acquired to cover all areas of the LA uniformly, excluding the left atrial appendage (LAA). All patients benefited from point-by-point radiofrequency energy in an antral circumferential ablation pattern around each pulmonary vein pair according to the CLOSE protocol (22) and guided by Ablation Index (Biosense Webster, Inc.) targets of 500 for the roof and anterior wall, and 350 for the posterior and inferior walls. All patients benefited from pulmonary vein isolation (PVI). Additional line ablation was performed at the physician's discretion.

Image processing and fibrosis quantification:

All image post-processing and measurements were performed using the Slicer3D software (version 4.13.0; <http://www.slicer.org>) and custom Python scripts. Raw 3D data of the atrial EAVM models was imported from the CARTO3 system. The CARTO3 system uses a triangular mesh with a voltage associated with each cell vertice. In order to make a comparison with the volumic information of PET-CT and LGE-CMR scans, we applied the following method. (figure 1) First, the walls of the left atrium are identified by outlining the endocardial and epicardial boundaries on axial slices, with help from MRA images. Then, a 3D surface model is created based on the shape of endocardial segmentation. Lastly, each point on the surface model was endowed with the highest SUV value (respectively highest LGE-CMR intensity) detected within the left atrium along the direction of the normal vector, by sampling the space between the endocardium and epicardium along this vector.

To calculate the global mean atrial voltage (V_{GLA}), we multiplied each cell area of the CARTO3 system triangular mesh by the mean of the bipolar peak-to-peak voltage amplitudes of its vertices. We then summed it for the whole atria excluding the pulmonary veins and the mitral valve, and divided the result by the total area. This process was repeated for voltage values recorded in atrial fibrillation and right atrial (RA) pacing at 100 b.p.m after electrical cardioversion.

To determine the extent of low voltage areas (LVA), we summed the area of cells for which the average of their vertices fell below the usual threshold of 0.30 mV during AF and 0.50 mV during RA pacing and divided the result by the total area. This provided the LVA extent without unit, expressed as a percentage of the LA surface as previously described (21). Patients were separated into 2 groups of LVA extent: LVA-Group I with absence or low LVA extent (LVA extent $\leq 15\%$), and LVA-Group II with moderate or extensive LVA extent (LVA extent $> 15\%$).

To determine the extent of LGE and atrial fibrosis by LGE-CMR, we adapted the calculation used for low voltage areas, utilizing the corresponding surface maps generated in the preceding steps. For fibrosis by LGE-CMR, we set the threshold at 2 standard deviations (SD) above the average intensity of the enhancement of blood signal. Meanwhile, for LGU, the threshold was established at 5 SD above the mean SUV of blood. AF-LGE was classified by Utah stages as I to IV as, respectively, atrial LGE of 0% to 10%, 10% to 20%, 20% to 40%, and $>40\%$ LGE. (17) To facilitate visual inspection and comparison, all models underwent co-registration using an iterative closest point algorithm. This algorithm included 12 degrees of freedom, allowing for deformation and scaling during the process.

Clinical Follow-up:

After the CA procedure, patients underwent clinical follow-up, ECG, and 24-hour ambulatory Holter monitoring at discharge, 3 months, 6 months, 1 year, 18 months, and 2 years. Additionally, patients received Remote Heart Rhythm Sampling with AliveCor Heart Monitor, enabling acquired iECGs thrice weekly for 30 seconds. Surface ECG, ambulatory ECG, and cardiac event recording were obtained when patients presented symptoms of arrhythmia recurrence. An experienced rhythmologist performed ECG data acquisition and analysis. Any detectable atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) of at least 30 sec beyond a 3-month blanking period after the procedure was considered a recurrence.

Statistical analysis.

All statistical analyses were conducted using SPSS version 26.0 (SPSS, Inc., Chicago, IL, United States) and R software version 3.5 (R-project, Vienna), with a p-value of $p < 0.05$ deemed statistically significant. Continuous variables were assessed for normality through Q-Q plots, histograms, and the Kolmogorov-Smirnov test. They were reported as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) based on their distribution. These variables were subsequently compared between patients and controls using the two-sided t-test or the Mann-Whitney U test, as appropriate. Categorical data were expressed as counts and percentages and were compared using the Chi-square test.

The relationship between the extent of LGU, LVA, LAVI and fibrosis as determined by late gadolinium enhancement-cardiac magnetic resonance was evaluated through linear regression analysis and the Pearson correlation coefficient. Uni- and multivariable binary logistic regression analyses were used to determine associative factors predicting LVA extent. Parameters with significant collinearity were not allowed to simultaneously enter the multivariable model. Collinearity was evaluated by multiple regression analysis between parameters, and we considered evident collinearity when tolerance ($1 - R^2$) was < 0.1 or variance inflation factor > 5 . To predict LVA extent and AF recurrence, receiver-operating characteristic (ROC) curves were plotted. Area under the curve (AUC) were compared with Delong test. Freedom from atrial fibrillation following CA were analyzed using Kaplan-Meier analysis for different thresholds of low glucose uptake area extent and using Cox multivariate analysis taking into account LA-indexed volume and the use of antiarrhythmic medication.

Supplementary appendix 2 – Additional results

EAVM were also generated during RA pacing in all patients before CA procedure, utilizing 1472 ± 861 acquired points and revealing median LVA extent of 11.69 % [6.61;22.15] and median V_{GLA} of 1.68 mV [1.48;2.26]. Table 5 A majority of patients, specifically 22 (61%), presented with LVA. Notably, LVA extent was found to be higher and V_{GLA} to be lower in patients with elevated levels of LGU ($P=0.002$ and $P=0.017$ respectively).

Although less good during RA pacing, quantitative analysis between LGU and LVA extent evaluated during RA pacing keep a good correlation of $R^2=0.35$ ($P<0.001$). Figure 7`

The relationship between EAVM and PET parameters is also illustrated by a good correlation between V_{GLA} and LA mean SUV ($R^2=0.35$; $p<0.001$). Figure 8

Finally, the ROC curves for the prediction of LVA extent acquire during RA pacing before the ablation procedure for the different noninvasive imaging parameters are shown in Figure 9. LGU Keep the highest area under the curve (0.77; 95% CI:0.58-0.96) for prediction of LVA extent > 10%, which was significantly higher than the AUC for LGE extent fibrosis (AUC=0.57; 95%: 0.34-0.79) or LAVI (AUC=0.61; 95% CI:0.40-0.82).

Table 5 Procedural characteristics during RA pacing

	All patients	LGU≤17%	LGU >17%	P value*
Voltage parameters during RA pacing				
LVA extent	11.69[6.61;22.15]	8.54[3.75;16.87]	15.87[10.53;26.11]	0.002
V_{GLA}, mV	1.68[1.48;2.26]	1.93[1.67;2.29]	1.51[1.28;1.93]	0.017

Table 5: Data are presented as mean±SD, number (percentage) or median [interquartile range].; LVA, low-voltage area; V_{GLA} , global left atrial voltage; RA, right atrial; LGU: low glucose uptake. P value* compare group LGU≤17% and LGU > 17%.

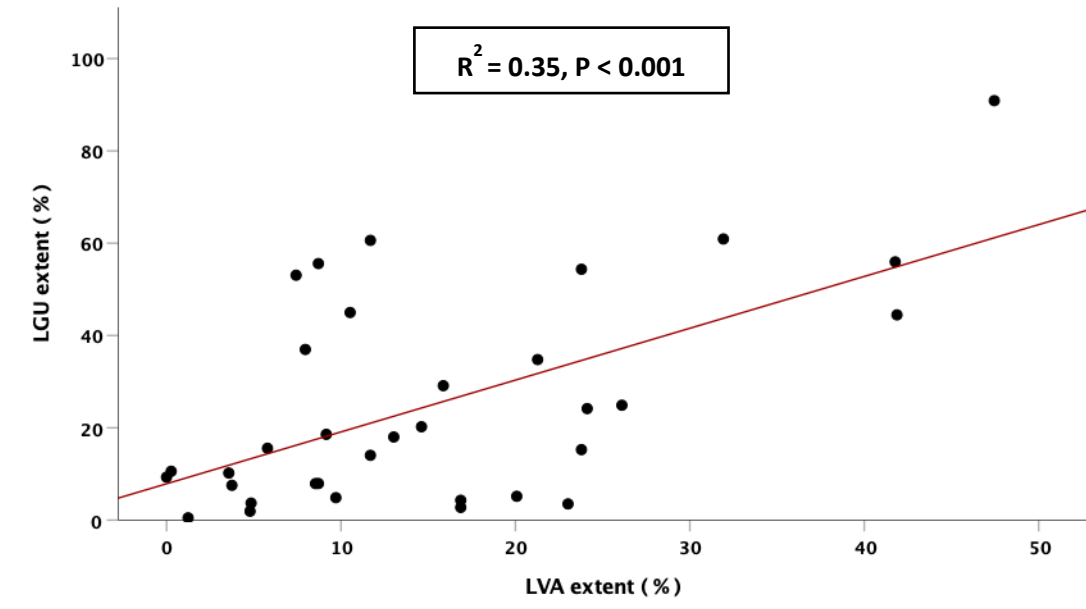


Figure 7: Correlation between LVA extent acquired with electroanatomical voltage map during right atrial pacing and LGU extent with ^{18}F -FDG positron emission tomography evaluated through linear regression analysis and the Pearson correlation coefficient. LVA: low voltage area; LGU: low glucose uptake.

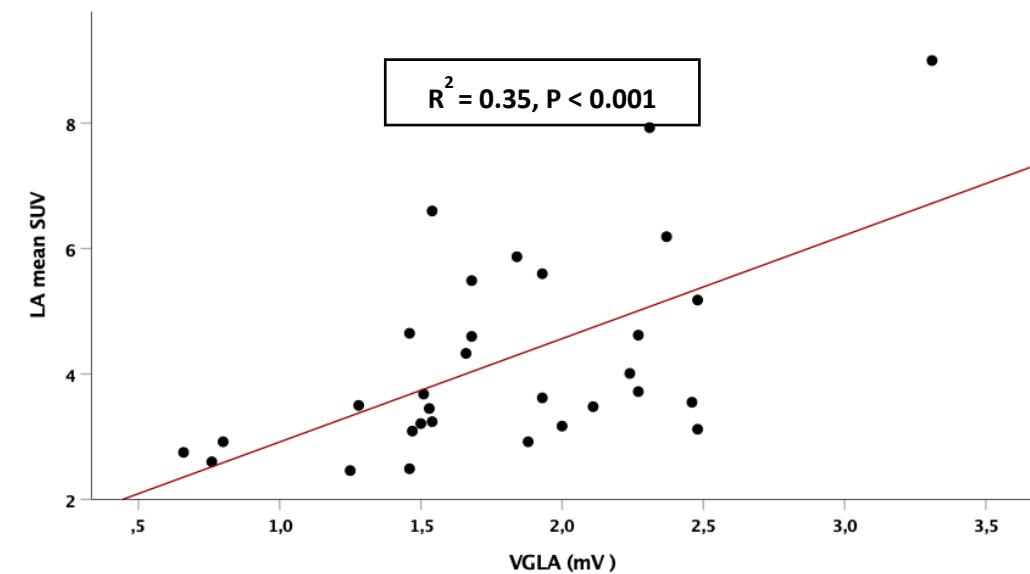


Figure 8: Correlation between global left atrial voltage acquired with electroanatomical voltage map during right atrial pacing and left atrial mean SUV with ^{18}F -FDG positron emission tomography evaluated through linear regression analysis and the Pearson correlation coefficient. LA: left atrium; SUV: standardized uptake value; V_{GLA}: global left atrial voltage.

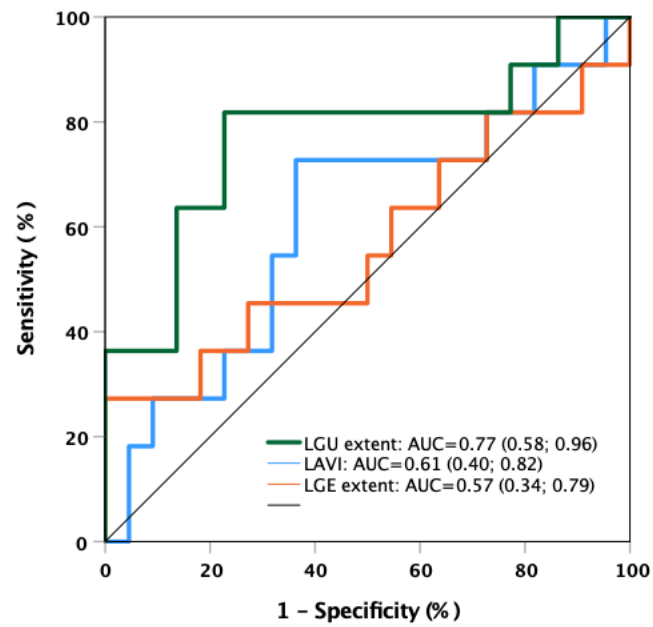


Figure 9: Receiver-operating characteristic curve analysis for prediction of LVA extent > 10% during EAVM acquired during right atrial pacing. AUC, area under the curve. LGU, low glucose uptake; LAVI, left atrium volume index; LVA, low voltage area; LGE, extent fibrosis detected with late gadolinium enhancement cardiac magnetic resonance imaging.

Supplementary appendix 3:

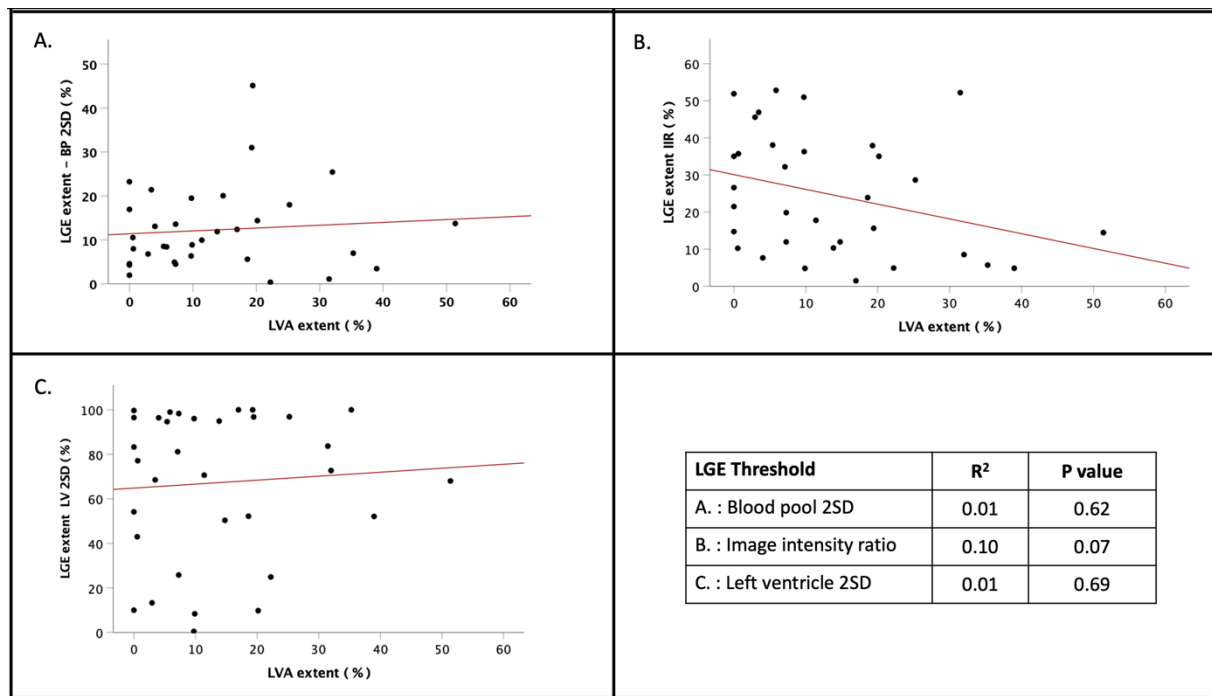


Figure legend: Correlation between LVA extent and LGE extent evaluated through linear regression analysis and the Pearson correlation coefficient, according to several LGE thresholds for defining atrial fibrosis and showing that they were no significant correlation between LVA and LGE by any methods. LVA: low voltage area with electroanatomical voltage map; LGE, late gadolinium enhancement with cardiac magnetic resonance imaging; BP, blood pool; IIR, image intensity ratio; LV, left ventricle; SD, standard deviation.

Figure legends

Figure 1

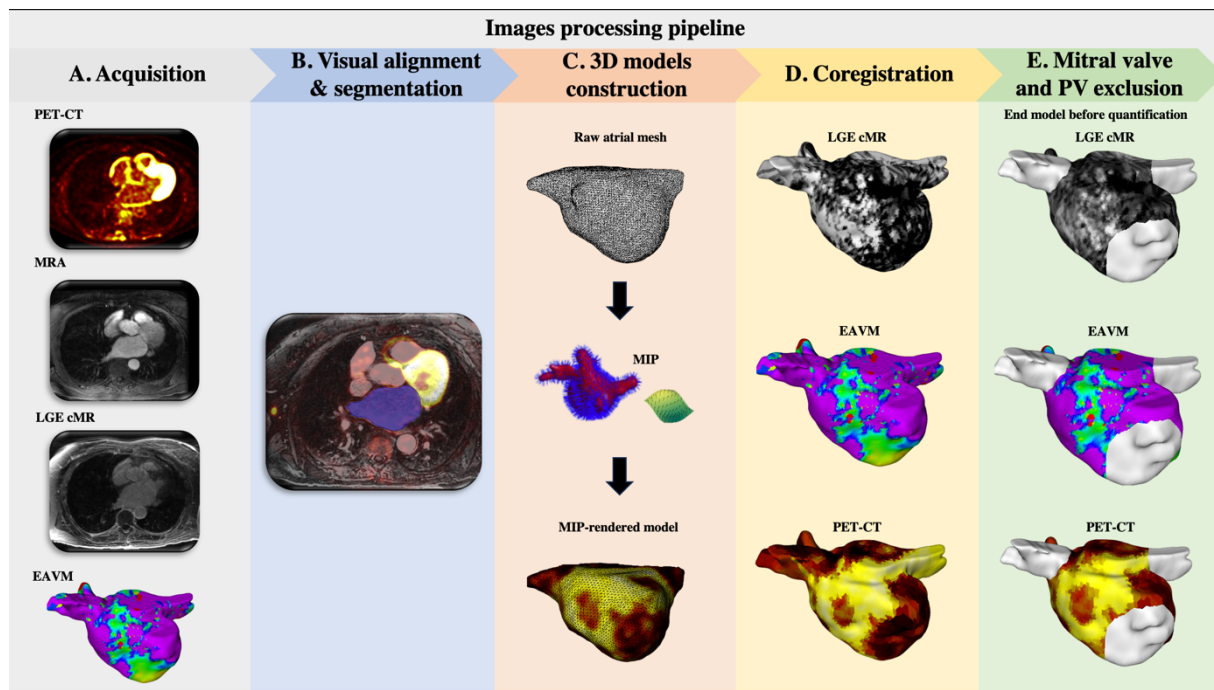


Figure 1: Workflow of the acquisition, alignment, segmentation and postprocessing of left atrial cMRI LGE, left atrial EAVM and left atrial ^{18}F -FDG-PET images. **A:** Images were acquired during AF before the ablation procedure (cMR - ^{18}F -FDG) and were at first visually aligned with cMR angiographic images. **B:** The segmentations of the LA in DE-cMR and PET were reformatted as 3D models. **C:** A maximum-intensity projection of the values inside the atrial wall was used to overlay the models. **D:** All models, including the EAVM, were then coregistered with a 3D model reconstructed from magnetic resonance angiography, using an iterative closest point algorithm (12 degrees of freedom, including deformation and scaling). This allows direct comparison by visual inspection. **E:** LGE fibrosis extent (cMR), LVA extent (EAVM) and LGU extent (^{18}F -FDG PET) were identified and quantified after excluding the mitral valve and pulmonary veins volumes. PET, positron emission tomography; MRA, magnetic resonance contrast-enhanced angiographic; LGE cMR: late gadolinium enhancement cardiac magnetic resonance; EAVM, electroanatomical voltage mapping; MIP, maximum intensity projection; PV, pulmonary vein.

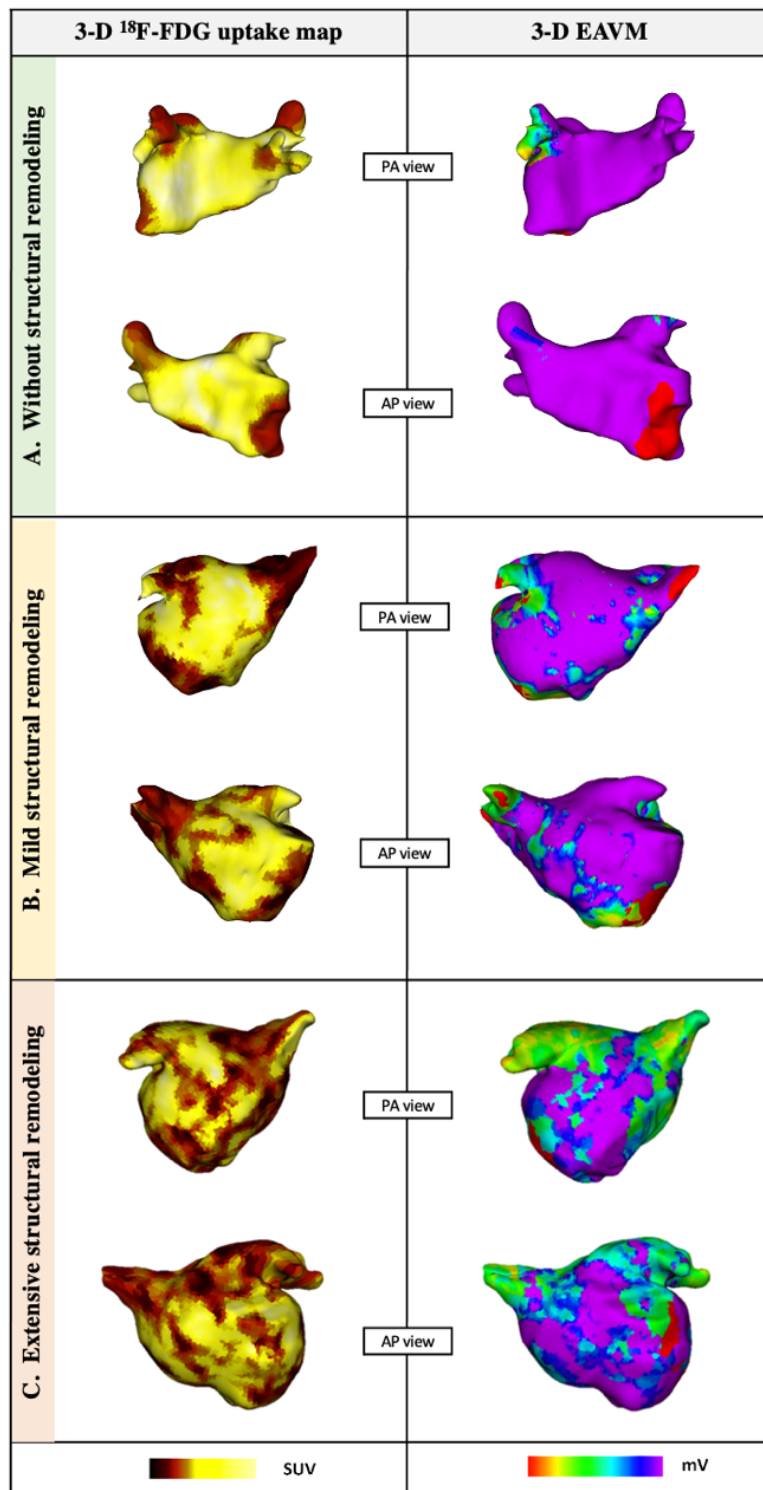


Figure 2: Segmented 3 dimensions (3D) ^{18}F -FDG uptake map relationship with 3D EAVM acquired during AF ablation procedure in PA and AP views. The color gradient of the LVA maps indicates endocardial electrogram amplitude from pink (>0.3 mV in AF) to red (at <0.1 mV). The color gradient of the LGU maps indicates ^{18}F -FDG standardized uptake value amplitude from dark/brown (LGU area) to yellow (without LGU area).

A: Illustration of a patient showing a homogenous distribution of the tracer without LGU extent in the LA wall. Color 3D EAVM show electrically normal atrial tissue without LVA.

B: Illustration of a LA with moderate remodeling, displaying a heterogeneous tracer distribution indicating LGU area in the posterior and inferior sections of the LA, particularly around the left inferior PV and right inferior PV ostia. LGU is also evident in the antero-septal region of the LA. Color 3D EAVM in the PA and AP views show abnormal atrial tissue with LVA in the corresponding region.

C: Illustration of a LA with extensive remodeling. Heterogeneity of the tracer distribution is more pronounced with significant LGU in the LA's posteroinferior, anterior, and antero-septal regions, corresponding on EAVM to abnormal atrial tissue with LVA.

^{18}F -FDG, ^{18}F -fluorodeoxyglucose; LGU, low glucose uptake; LVA, low voltage area; EAVM, electroanatomical voltage mapping; PV, pulmonary vein; PA, posteroanterior view; AP, anteroposterior views; SUV, standardized uptake value. mV, millivolts.

Figure 3

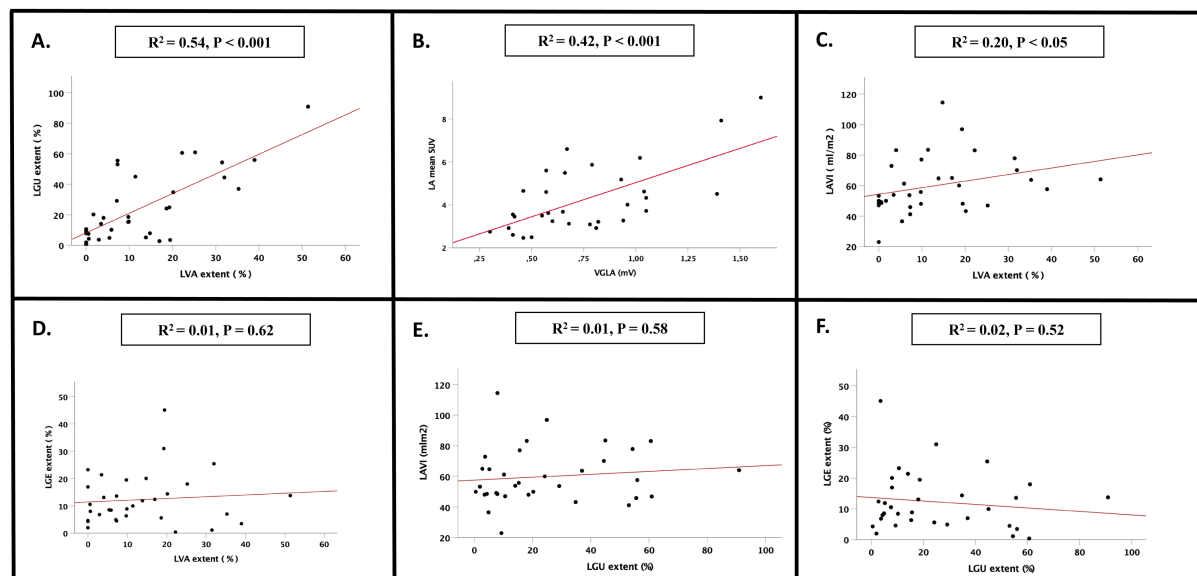


Figure 3: Correlation between the different imaging modalities evaluated through linear regression analysis and the Pearson correlation coefficient. LGU: low glucose uptake; LVA: low voltage area with electroanatomical voltage map acquired in atrial fibrillation; LGE: late gadolinium enhancement with cardiac magnetic resonance imaging; LAVI: left atrial volume indexed with trans-thoracic echocardiography; V_{GLA} : global left atrial voltage acquired in atrial fibrillation.

Figure 4

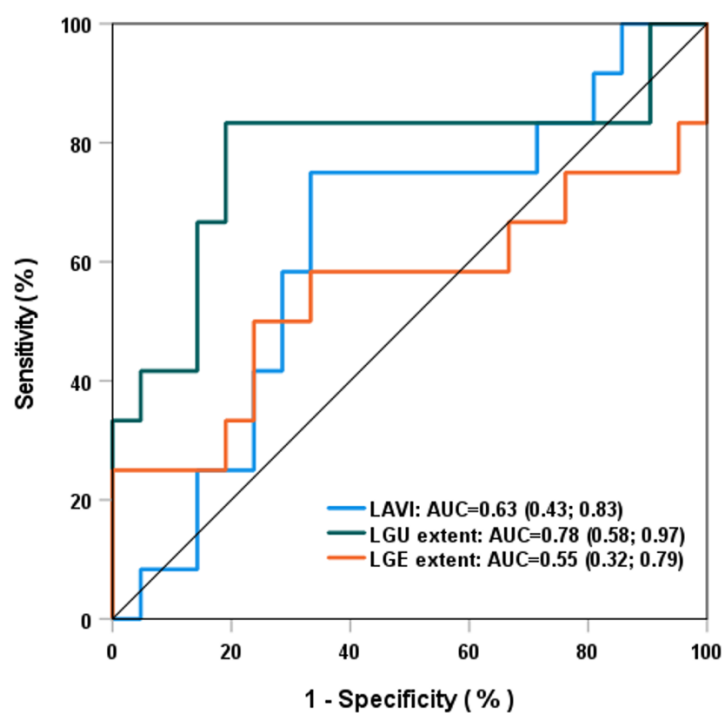


Figure 4: Receiver-operating characteristic curve analysis for prediction of moderate or extensive LVA during EAM. AUC, area under the curve. LGU, low glucose uptake; LAVI, left atrium volume index; LVA, low voltage area; LGE, extent fibrosis detected with late gadolinium enhancement cardiac magnetic resonance imaging.

Figure 5:

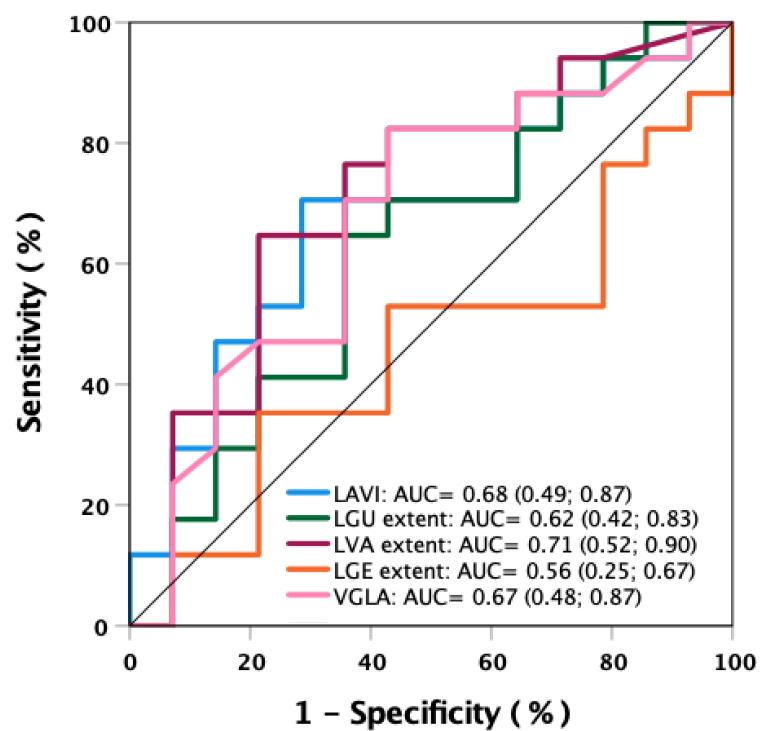


Figure 5: Receiver-operating characteristic curve analysis for prediction of atrial fibrillation recurrence after catheter ablation. AUC, area under the curve. LGU, low glucose uptake; LAVI, left atrium volume index; LVA, low voltage area; LGE extent, fibrosis detected with late gadolinium enhancement cardiac magnetic resonance imaging. V_{GLA}: global left atrial voltage acquired in atrial fibrillation.

Figure 6:

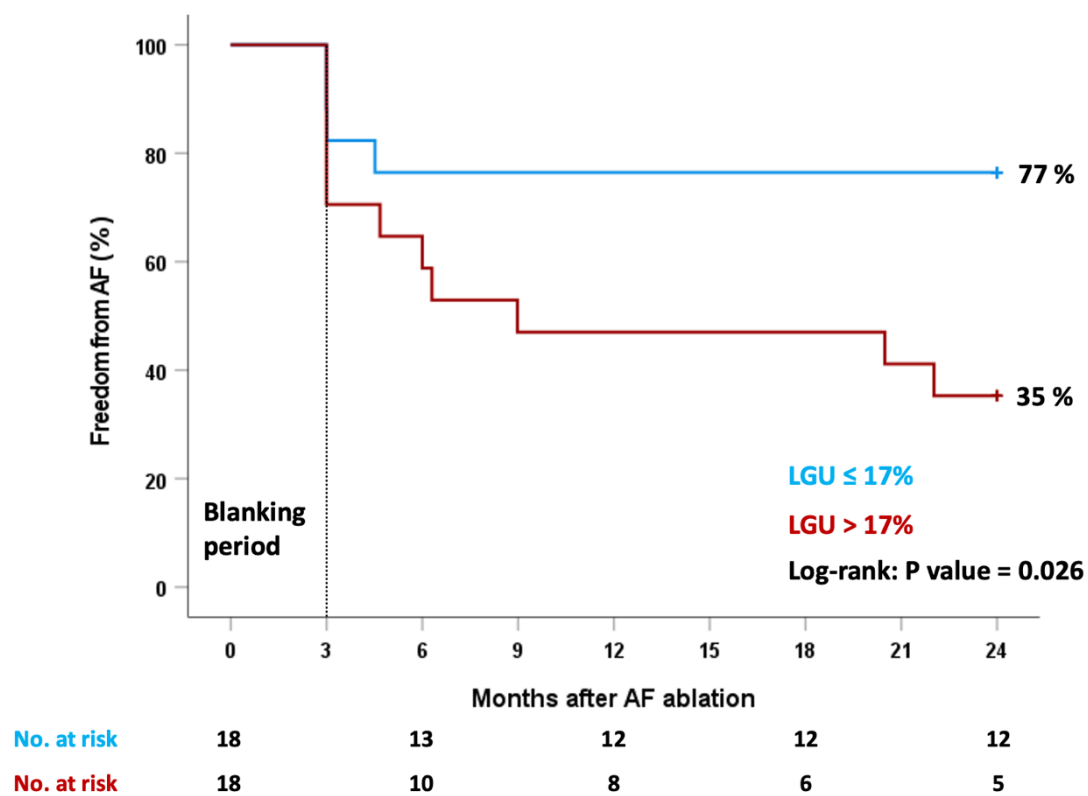
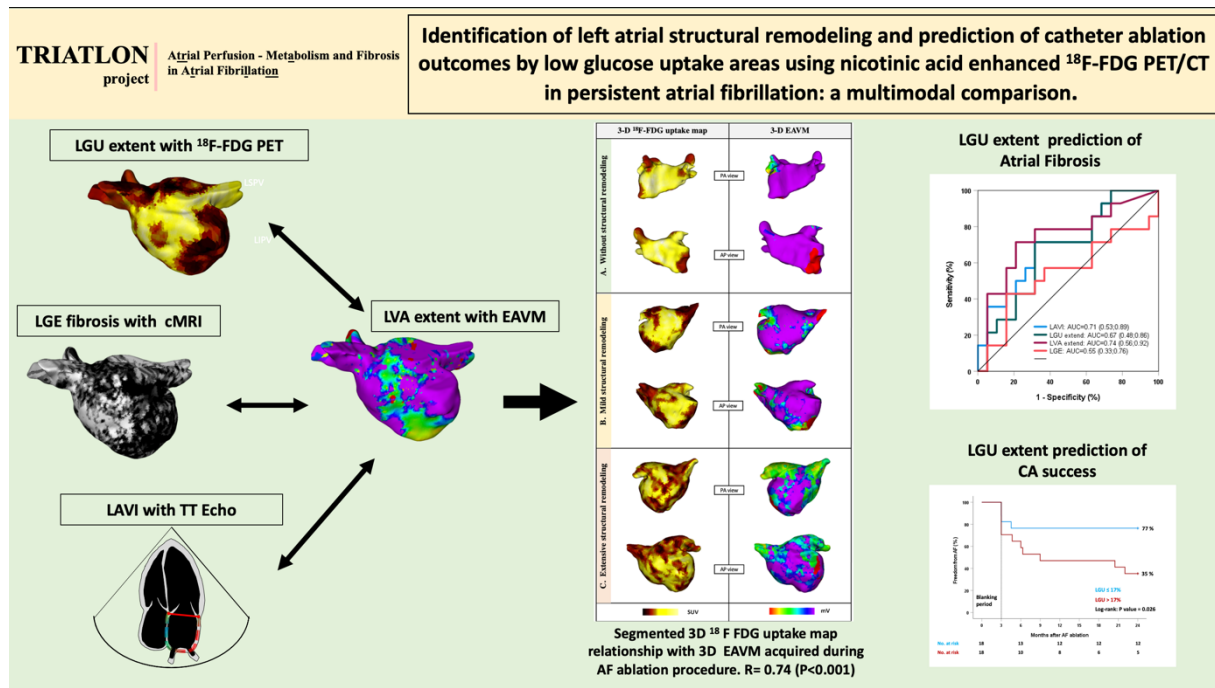


Figure 6: Kaplan–Meier estimates of freedom from documented atrial fibrillation more than 30 seconds after AF ablation procedure according to LGU extent, with or without the use of antiarrhythmic medications. AF, atrial fibrillation; LGU, low glucose uptake.

Structured graphical abstract:



Structured graphical abstract: Multimodal imaging comparison of nondiabetic patients with persistent non valvular atrial fibrillation showing a good correlation between Segmented 3 dimensions (3D) ^{18}F -FDG uptake map and 3D electroanatomical voltage map acquired during AF ablation procedure. The result show that, among the non-invasive imaging modalities, LGU extent quantification with ^{18}F -FDG PET in the left atrial walls had the highest diagnostic accuracy for predicting LVA extent and independently allowed to predict the success of CA procedure in persistent AF patient. LGU, low glucose uptake; ^{18}F -FDG PET, ^{18}F -fluorodeoxyglucose positron emission tomography; LVA, low voltage area; EAVM, electroanatomical voltage mapping; LGE cMR: late gadolinium enhancement cardiac magnetic resonance; LAVI, left atrium volume index; CA, catheter ablation.

Appendices

Supplementary appendix 1: detailed methods.

Supplementary appendix 2: summary of data acquired during RA pacing.

Supplementary appendix 3: Correlation between LVA extent and LGE extent evaluated through linear regression analysis and the Pearson correlation coefficient, according to several LGE thresholds for defining atrial fibrosis.

- CHAPTER IV -
- CONCLUSIONS AND PERSPECTIVES -

4. CHAPTER IV: CONCLUSIONS AND PERSPECTIVES

CONCLUSIONS:

Persistent AF remains a challenge for the clinician because its pathophysiology and its relationship with atrial cardiomyopathy and LA remodeling are complex and multifactorial. Previous work showed that this arrhythmia is characterized by irregular high-frequency excitation and contraction that affect atrial energy demands, resulting in metabolic stress. This metabolic imbalance increases glucose uptake and influences the development of LA remodeling which predict persistence of AF. Recent ESC guidelines confirm that characterization of AF including evaluation of substrate and atrial cardiomyopathy should be considered in all AF patients for optimal management. Several tools exist to evaluate atrial substrate and each imaging technique has advantages, limitations, and pitfalls.

In this area, the TRIATLON project; 1) confirms the role of echocardiography and STE as a first-line imaging modality; 2) highlights an emerging tool, the ^{18}F -FDG PET/CT, with an innovative and original approach by evaluating atrial arrhythmogenic remodeling through the glucose metabolism and the metabolic stress evaluation induced during AF.

- **Trans-thoracic echocardiography and STE.** Our work shows that during AF, echocardiography and speckle tracking echography parameters with LAVI, E/e', GPALS, and LA stiffness independently allowed to predict LVA during electro-anatomical mapping. Of all the parameters, LA stiffness had the highest diagnostic accuracy for the prediction of LVA. In addition, low GPALS and elevated LA stiffness are also able to predict the success of CA procedures and maintenance of SR with similar accuracy as LVA extent. For this purpose, the predictive accuracy of GPALS is significantly better than the APPLE score and LAVI.

This supports the use of STE to non-invasively predict the severity of atrial fibrosis and the success of ablation procedures in patients with persistent AF. Nevertheless, echocardiography does not allow a direct and quantitative analysis of the LA fibrosis extent and does not provide a physiopathological explanation for its development process. This confirms the interest of a multimodal approach for the evaluation of LA remodeling.

- ¹⁸F-FDG PET/CT: The interest of PET in the field of AF to evaluate atrial myopathy is emerging with different protocols. Retrospective and prospective studies have evaluated FDG uptake using strategies to suppress physiological myocardial FDG uptake by prolonged fasting, dietary manipulation, and heparin loading and have shown that the FDG Uptake was related to the increased activity of atrial structures and EAT and inversely correlated with LA fibrosis. However, the interpretation of FDG uptake is complex and, in these studies, in the absence of histological confirmation it was impossible to know whether the atrial FDG activity measured corresponds to the metabolic activity in atrial wall, in the EAT or both. In our study, the patient sample was homogeneous, all patients were in persistent AF during the first PET, the protocol and the uptake interpretation were different. Patients received a similar preparation used to evaluate myocardial viability in coronary heart disease with a nicotinic acid derivative (Acipimox) after overnight fasting to maximally stimulate myocardial glucose uptake.

In this protocol, we demonstrated that the Philips Vereos time of flight-PET/CT images reconstructed with the manufacturer four iterations/15 subsets ordered subset expectation maximization algorithm including a point spread function resolution recovery with five iterations/six regularization can be used to obtain successfully a 3-D map LA - ¹⁸F-FDG uptake. These parameters allowed visualization and analysis of several structure such as fossa ovalis, mitral annulus, PV ostia or LAA with sufficient spatial resolution, arguing for this map corresponds to a reliable replica of the LA wall anatomy and not EAT.

Under these metabolic conditions which favor glucose utilization by cardiomyocytes, we showed that patients with persistent AF present increased LA and LAA ¹⁸F-FDG uptake relative to healthy controls, while the ¹⁸F-FDG uptake in the LV was similar. Moreover, after return to SR, under similar conditions and with similar LV ¹⁸F-FDG uptake, LA and LAA FDG uptake decreased significantly, despite improvement of LA contractile function.

Previous in vivo observations supported the existence of an atrial cardiomyopathy where altered atrial metabolism is a component of both AF initiation and progression. Indeed, the metabolic wasting might lead to ischemia or hibernation status, resulting in myocyte necrosis and apoptosis and subsequent replacement of the tissue by fibrosis. Our study directly support that such metabolic alterations highlighted by FDG imaging in patients with persistent AF are involved in the atrial cardiomyopathy process and illustrate the "AF begets AF" concept.

Finally, we observed that low glucose uptake areas on nicotinic acid enhanced ^{18}F -FDG PET in patients with persistent AF closely correlated with areas of electrical low voltage area during EAVM indicating that LGU detects left atrial fibrosis. Furthermore, the spatial extent of LGU predicted the success after CA procedure indicating that this parameter can non-invasively evaluate the severity of atrial structural remodeling in atrial cardiomyopathy. These findings support the potential role of ^{18}F -FDG-PET in improving the evaluation and management of patients with persistent AF candidates for AF ablation procedures.

PERSPECTIVES

During a conference organized in our establishment, professor Michel Haïssaguerre summarized the future of research in AF in 3 points:

1. Demonstrate the benefits of SR in terms of thromboembolic events, hemodynamic, dementia and QOL.
2. Optimize curative treatment: tool-energy-lesion assessment.
3. Prevent substrate constitution (risk factors) in persistent AF and drug prevention of PV firing.

Our work focuses on the third pillar of this reflection.

Besides providing further insights into the pathophysiology of AF, our study demonstrates the feasibility of acipimox-enhanced FDG PET for high-quality atrial imaging *in vivo*. This technique may be comparable to LGE cMR and other imaging techniques, potentially providing clinical applications in evaluating atrial remodeling prior to catheter ablation procedure with a noninvasive method for quantifying and localizing LA remodeling. This suggests that studying atrial metabolism hold promises for guiding physicians and deepening our understanding of atrial remodeling during persistent AF since FDG-PET uptake could serve as an indication of preserved atrial myocyte function, thereby demonstrating the absence of atrial fibrosis.

Further research should investigate:

- The potential utility of this non-invasive imaging technology in clinical practice with largest population including diabetic patient in order to confirm the correlation between ^{18}F -FDG-PET uptake and AF structural remodeling or atrial cardiomyopathy, to guide AF ablation strategies and predict the outcomes of AF ablation procedures.
- The interest of next PET camera technologies to provide more detailed and precise analysis of the LA wall with better image resolution.

Moreover, FDG could help us to open avenues for reflection to improve our understanding of the mechanisms involved in the pharmacological prevention of atrial cardiomyopathy with new drugs.

Finally, this work raises as many intriguing questions as it answers others:

- We assumed that LA uptake reflects glucose uptake in the cardiomyocyte but could part of this uptake be influenced by macrophage uptake and partly reflect inflammatory activity in the atrial wall?
- What about FDG uptake in the right atrium and how does it contribute to the pathophysiology of atrial cardiomyopathy process?
- Could we evaluate other tracers with other protocols to evaluate other metabolic or inflammatory pathways and interrogate other regions of interest? As proposed at the beginning of the project, could we associate the FDG of NH_3 to evaluate atrial perfusion and might have value to non-invasively detect atrial viability? Finally, recently, Gallium-68 fibroblast activation protein inhibitor (^{68}Ga -FAPi) PET targeting FAP-alpha was evaluated after PVI procedure in a proof-of-concept study. (185, 186) This protein is expressed by activated fibroblasts which are the main contributors to tissue remodeling. In the future, could this tracer help us improve our understanding of the atrial cardiomyopathy process in AF patients?

These questions cannot be adequately answered until more studies shed light on the topic, the most practical solution appears to be study and integration of various clinical, electrophysiological, biochemical, imaging and histological parameters.

- CHAPTER V – REFERENCES -

5. CHAPTER V: REFERENCES

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