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REVIEW ARTICLE

Atrial Remodeling in Atrial Fibrillation. Comorbidities and Markers of Disease Progression Predict Catheter Ablation Outcome

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Abstract: Atrial fibrillation is the most common supraventricular arrhythmia affecting an increasing proportion of the population in which mainstream therapy, *i.e.* catheter ablation, provides freedom from arrhythmia in only a limited number of patients. Understanding the mechanism is key in order to find more effective therapies and to improve patient selection. In this review, the structural and electrophysiological changes of the atrial musculature that constitute atrial remodeling in atrial fibrillaton and how risk factors and markers of disease progression can predict catheter ablation outcome will be discussed in detail.

Keywords: Atrial fibrillation, atrial remodeling, fibrosis, predictors of catheter ablation outcome, electrophysiological remodeling, scar imaging.

1. INTRODUCTION

Atrial fibrillation (AF) is a disease with a growing incidence, affecting large segments of the population worldwide and having a profound effect on morbidity, mortality, and the quality of life. Therapies that are truly effective in all categories of patients have yet to be discovered. The key to progress, aside from critical technological advances, is to gain mechanistic insights into the initiation and perpetuation of AF to identify upstream therapies, such as the ones targeting profibrotic signaling systems.

Atrial remodeling in AF is the reorganization of atrial anatomy, microstructure and function (impulse generation and conduction as well as myocardial contraction) that can be attributed to systemic (aging, hypertension, *etc.*) and local factors (valvular disease, cardiomyopathy, *etc.*) (Fig. **1**). Extensive research is focusing on the nature of remodeling of the atrial musculature and how risk factors contribute to it in order to discover opportunities for intervention.

It was previously hypothesized that since the foci that initiate AF are located in the pulmonary veins (PVs), perfecting the technique to isolate them would prevent further episodes. In a population of paroxysmal AF patients, Taghji *et al*. demonstrated that using contact force catheters and achieving certain ablation targets resulted in durable RF lesions and a remarkable 12-month ablation success [1]. However, PV isolation has been proven to be insufficient in patients with long-standing persistent AF [2-4] and there are reports of AF recurrence despite durable PV isolation [5, 6] that underpin the idea of progressive remodeling of the atrial myocardium and the importance of extra PV sources of AF initiation and maintenance. Understanding the complexity of the substrate should be the basis of personalized treatment and provide a perspective on ablation outcome and managing patient expectations.

2. ATRIAL REMODELING – CHANGES IN THE HISTOLOGY AND ELECTROPHYSIOLOGICAL PROPERTIES OF THE ATRIAL MYOCARDIUM

Fibrosis is a normal process meant to preserve the structure of an organ or system in response to injury and is a key element in the pathogenesis of AF, as it is known to cause non-uniform impulse propagation, re-entry and to anchor drivers. There is evidence showing that fibrillatory activity is linked to fibrotic areas of the atrial microstructure, the posterior left atrium and specifically the antrum of the PVs [7] representing a common localization of AF sources, as opposed to the left atrial (LA) anterior wall showing the least fibrosis [8].

Atrial remodeling is a result of systemic (obesity, hypertension) as well as local processes (atrial wall stretch, activation of platelets, myocardial infarction) causing an inflammatory reaction that involves oxidative stress, alterations in Ca-regulation [9], production of pro-inflammatory cytokines, proliferation of fibroblasts and myofibroblasts expressing α-smooth muscle actin (α-SMA) as well as extracellular matrix (ECM), resulting in a build-up of fibrotic tissue favoring the development and maintenance of AF [10]. Furthermore, ongoing AF has been shown to lead to atrial enlargement and

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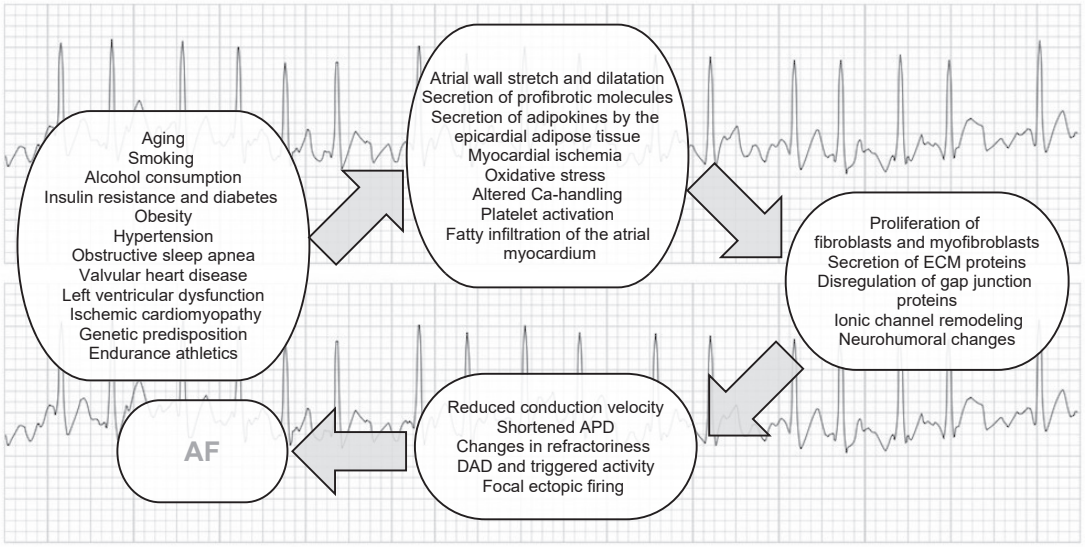

Fig. (1). Pathogenesis of AF: Risk factors lead to the structural and electrophysiological remodeling of the atria. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

functional mitral regurgitation (MR) [11] and an increase in the extent of the epicardial fatty tissue [12, 13].

2.1. Inflammation and Profibrotic Signals

Inflammatory cell infiltration, such as of macrophages, neutrophils, and monocytes, plays an important role. Frustachi *et al*., described lymphomononuclear infiltrates with necrosis of the adjacent myocytes in his histological study [14] and Oishi *et al*., showed that atrial stretch *in vitro* induced macrophage migration *via* increases in ATP in the gap junction channels [15]. Furthermore, there is evidence suggesting that pro-inflammatory macrophage polarization leads to atrial electrical remodeling *via* IL-1β secretion [16]. Profibrotic signals, such as transforming growth factor beta1 (TGFβ1) and platelet-derived growth factor (PDGF) act on cell membrane receptors that lead to the activation of mitogen-activated protein kinases. These promote the production of ECM proteins, enzymes that process them as well as signaling molecules that further promote fibrosis. Nattel and colleagues discerned two types of fibrotic changes: reactive (interstitial) fibrosis where there is an increase in fibroblasts, myofibroblasts and ECM in the perivascular space and around myocardial bundles without substantial changes in myocardial architecture and replacement (reparative) fibrosis where damaged myocytes are replaced by fibrotic tissue, fundamentally changing the electrophysiological properties of the myocardium [17].

2.2. Fibrosis

In AF patients awaiting mitral valve surgery, Corradi *et al*. revealed interstitial fibrosis, a decrease in capillary density and alterations in myocyte morphology and distribution, including loss of sarcomeres, dedifferentiation of myocytes into myofibroblasts, as well as evidence of perinuclear myocytolysis and changes in mitochondrial shape [18]. Markers of collagen degradation, procollagen III N-terminal propeptide (PIIINP), and type I carboxy-terminal telopeptide (ICTP) have been shown to be associated with incident AF in The Multi-Ethnic Study of Atherosclerosis – a patient population free of heart diseases [19].

2.3. Myofibroblasts

The interplay of fibroblasts and myocytes has a pivotal role in atrial remodeling. Fibroblasts secrete autocrine and paracrine factors as well as ECM proteins and have an important role in response to cardiac injury [20]. Myocytes, on the other hand, produce reactive species of oxygen, PDGF, and TGF-β stimulating fibroblast proliferation and differentiation. Myofibroblasts are fibroblasts that exhibit an increase in the alpha-smooth muscle actin, especially at the transition from paroxysmal to persistent AF. They become contractile, express adhesive proteins, and by coming in contact with myocytes, they promote their dedifferentiation. They interact with each other through gap junction proteins, such as CX43, myocyte action potentials generating small electrotonic potentials in myofibroblasts [21]. Zlochiver *et al*. conducted numerical simulations in a two-dimensional rat myocyte-myofibroblast coculture in order to reconstruct the consequences of myocyte-myofibroblast electrical coupling through gap junctions. Increasing the myofibroblast ratio decreased re-entry frequency, slowed conduction velocity, and promoted wave fractionation, increasing intercellular coupling stabilized rotors and enhanced the conduction velocity [22]. It is important to note that heterocellular electrical coupling was demonstrated *in vitro*, but not *in vivo*.

2.4. Gap Junction Proteins

Gap junction proteins, connexins, are located at the intercalated discs of myocytes and cells of the conductive tissue. Connexins Cx43, Cx45, and Cx40 [23] have an important role in cardiac myocyte to myocyte interaction and are essential for impulse propagation and determine conduction velocity. As noted above, they also link fibroblasts and fibroblasts to myocytes. In an elegant study, van der Velden *et al*. char-

acterized the gap junction remodeling in AF, looking at the main connexin of the atria and the conduction system, CX40, as well as CX43. They found that although CX40 mRNA levels where unchanged, CX 40 protein levels decreased with Western Blot and there was a heterogeneous distribution of CX40, but not of CX43 with stabilization of AF in the atria of goats [24].

The idea of longitudinal dissociation as a basis for arrhythmia generation and maintenance was put forward a couple of decades ago [25]. Alessie *et al*. demonstrated its validity in persistent AF with high density epicardial mapping and wave analysis, showing it to be a consequence of fibrosis separating bundles of muscle fibers along their longitudinal axis and interfering with the side-to-side conduction of impulses. In paroxysmal AF, they found broad wavefronts often colliding, while in persistent AF, impulse propagation occurred *via* narrow channels bound by dynamically shifting lines of block parallel with the orientation of the fibers [26].

2.5. Cardiac Adipose Tissue

There are reports explaining, in detail, the role of cardiac adipose tissue in the pathophysiology of AF. Haemers *et al*. showed that among patients undergoing cardiac surgery, permanent AF was associated with more extensive fatty tissue compared to paroxysmal AF and no history of AF. These findings are supported by their sheep long-term tachypacing model of AF, where the induction of AF resulted in a significant increase of the left atrial epicardial adipose tissue [27]. Adipocytes are thought to secrete adipokines that induce atrial remodeling. Venteclef *et al*. demonstrated that adding the secretome of human epicardial adipose tissue to the organo-culture of the adult rat atrium induced fibrosis and the production of Activin A, member of the TGF-β family [28].

2.6. Altered Calcium-handling

Voight and colleagues studied the role of altered calcium (Ca)-handling in the pathophysiology of chronic AF, showing evidence of a diastolic Ca-leak (an increase of 50%) in human RA samples. It was linked to the hyperphosphorylation of Ryanodine receptor 2 (RyR2) channels with increased open probability and upregulation of RYR2 regulatory proteins. They found that the increased Ca^{2+}-release from the sarcoplasmic reticulum coupled with the upregulation of the sodium-calcium exchanger (NCX) lead to a transient inward current that caused delayed after depolarizations (DAD) and triggered activity. Furthermore, under experimental conditions, knock-in mice with constitutively phosphorylated RyR2 exhibited more Ca^{2+} sparks and enhanced susceptibility to pacing-induced AF compared to controls [29]. Ca^{2+} sparks and Ca^{2+} waves were visualized in AF patients undergoing cardiac surgery more frequently than in patients in sinus rhythm, while spontaneous inward NCX current frequency was significantly increased as well [30]. RyR2-leaks have been associated with the progression of AF, as evidenced by a study by Li and colleagues on cardiomyocyte-directed expression of the transcriptional repressor CREM-IbΔC-X (CREM-TG) in transgenic mice that exhibited an enhanced diastolic Ca^{2+}-release. The mice had a propensity to develop atrial ectopy at first, then atrial fibrillation in addition to atrial dilatation. The genetic inhibition of CaMKII-phosphorylation of RyR2 (CREM: S2814A mice) prevented the emergence of sustained AF. Furthermore, the normalization of RyR2-dependent Ca^{2+}-release halted atrial dilatation and atrial conduction abnormalities involved in the generation of AF as evidenced by optical mapping. Although there were some features of the model inconsistent with established human AF pathophysiology, namely the prolongation of APD due to ICa, L gain-of-function, the expression of this transcriptional repressor was increased almost 2-folds in atrial samples from AF patients [31]. The role of RyR2 Ca^{2+}-leaks is underpinned by the higher incidence of AF, sinus node dysfunction (SND), and inducible atrial arrhythmias during EP study (EPS) in patients with catecholaminergic polymorphic ventricular tachycardia CPVT [32].

2.7. Oxidative Stress

Oxidative stress starts shortly after the initiation of AF by the formation of free reactive oxygen species. Super-oxide generating enzymes nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX2/4) are one of the central players in the cardiovascular system that have a role in the pathogenesis of chronic metabolic disorders, such as hypertension, atherosclerosis, diabetes mellitus [33] and are involved in atrial fibrillation as well [34], mainly in the early stages. Reilly *et al*. showed that in long-standing AF, however, uncoupled nitric oxide synthase and mitochondrial oxidases are responsible for reactive oxygen species (ROS) production [35]. Oxidative stress contributes to the electrical remodeling of the atria via the reduction in the L-type Ca current and the increase in inward rectifier K current (IK1) that shorten both the action potential and repolarization [36]. It has been shown to cause calcium overload via oxidation of the Ryanodine Receptor (2RyR2) as well [37].

2.8. MicroRNAs

MicroRNAs are small non-coding RNA molecules that degrade specific mRNAs, and as a result, they decrease the transcription of the respective proteins. They are known to play a role in growth and differentiation, cell death, and metabolic control and are regarded as paracrine factors [38]. Their role in cardiovascular disease is exemplified by the microRNA miR-21 involved in the pathophysiology of myocardial hypertrophy and fibrosis as well as AF and by MiR-328 that induces downregulation of the L-type Ca channels by suppression of translation and destabilization of mRNA [39]. Furthermore, upregulation of Kir 2.1, causing an increase in IK1 current as a result of decreased miR-1, miR-26, and miR-101 levels, has been shown to lead to a shortening of action potential duration (APD) that promotes perpetuation of AF.

2.9. Role of the Autonomic Nervous System in AF

The activation and interplay between vagal and sympathetic activation have been shown to promote AF in animals as well as human studies. While risk factors for the initiation of AF, such as obesity, hypertension, and obstructive sleep apnea (OSA), lead to the activation of the autonomic nervous system, it is thought that AF itself modulates the sympathetic and vagal response [40]. β-adrenergic activation leads to

intracellular Ca-overload and DADs as well as increases in IK_{ur}, IK_s, and IK_{ACh} currents, while α-adrenergic activation inhibits I_{to}. The parasympathetic nervous system, on the other hand, *via* the cholinergic muscarinergic receptors inhibits ICaL and If currents and activates IK_{Ach}, shortening the ERP [41]. Impaired baroreflex sensitivity [42], stimulation of the carotid bodies causing a sympathetic surge [43], renal nerves [44], as well as ganglionated plexi [45] likely all play a role in AF pathophysiology.

2.10. Electrophysiological Remodeling

The electrophysiological remodeling of the atria comprises changes in both excitation and conduction properties. The action potential duration is shortened due to the remodeling of the L-type Ca-current (shortening the plateau phase) and the inward rectifier K^+ current (IK1) (affecting the terminal phase of repolarization) that results in promotion of re-entry [36]. The agonist-induced muscarinic receptor mediated K current (IKAch), which is known to shorten the APD, is decreased in AF (50% decrease in channel density compared to sinus rhythm) presumably to counteract the APD reduction detailed above [46]. Impulse conduction is slowed because of the discontinuous, zig zag propagation due to fibrosis, ion channel changes, and the downregulation of gap junction proteins (connexins) resulting in tissue heterogeneity.

The timeline of the above changes is highlighted in an ovine tachypacing AF model published by Martins *et al*. [47]. They showed that the rate of increase in the dominant frequency (DF) of fibrillatory activity predicted the transition from paroxysmal AF to persistent AF. During that transition, the DF of AF increased progressively along with changes in the electrophysiological properties of the atrial myocardium, followed later by signs of morphological remodeling, atrial dilatation, mitral regurgitation, patchy fibrosis of the posterior left atrium (LA) and myocyte hypertrophy. They recorded a reduction in APD and impaired rate adaptation of APD evoked by changes in the expression of ion channel proteins for the INa, ICaL, and K currents. Inward rectifier potassium current (IK1) current increased 2-3-fold, but only in long-standing persistent AF. They asserted that the changes in ion channel gene expression bring about the increase in DF of the fibrillatory activity.

2.11. Monogenic Ionic Chanel Mutations in AF

Monogenic mutations of ionic channels have been shown to promote AF, such as gain of function mutations of KCNQ1 (coding the α subunit of the IKs current) [48], SNC5A (sodium channel) [49], KCNH2 (hERG) [50] as well as nitric oxide synthase 3 (NOS3) [51] involved in autonomic regulation [52] and modulating ICaL [53].

2.12. P-wave Morphology and PR Prolongation

The surface ECG can be telling as well, specifically abnormal P-wave morphology and PR prolongation and their association with single-nucleotide polymorphisms (SNPs). In a genotype study involving 660 patients with paroxysmal and persistent AF awaiting catheter ablation, Husser *et al*. showed that 13 SNPs identified with genome-wide association studies (GWAS) [54-57] to be related to PR prolongation, integrin subunit alpha 9 (ITGA9), and SOX5, and were significantly associated with left atrial low voltage areas and changes in left atrial diameter. They were also shown to have an effect on the outcome of catheter ablation. While SOX5 encodes a transcription factor with a role in cell proliferation and maturation in a number of tissues influencing amongst other things myogenesis [58], ITGA9 is thought to be involved in regulating the expression of the gene SCN5A [57].

2.13. Activation of the Layers of the Atrial Myocardium During AF

De Groot *et al*. drew attention to the significance of asynchronous activation of the endocardial and epicardial layers of the atria and to the transmural propagation of wavefronts in sustaining atrial fibrillation in their *in vivo* RA simultaneous multielectrode endocardial and epicardial mapping study [59]. They hypothesized that AF maintenance, apart from re-entry and focal mechanisms published in the literature, can also be due to the layers of atrial myocardium constantly activating each other. Intramural re-entry was demonstrated using high resolution complementary metal oxide semiconductor (CMOS) cameras to map activation and 3 D GE MRI to map atrial wall structure, transmural fiber orientation, and interstitial fibrosis in a study published by Hansen and colleagues [60]. They examined coronary perfused right atria from explanted hearts and found that AF was maintained by spatially and temporally stable intramural circuits with an activation delay averaging 67 ms. The activations occurred alongside myocardial bundles isolated by fibrosis and identified with MR imaging, and they found that reentrant circuits were more often visualized on the endocardial surface, whereas breakthroughs on the epicardial. The highest DF zones were selected and the driver region was targeted with ablation in 5 hearts successfully terminating it. There are notable differences in the endocardial-epicardial activation in different stages of AF as evidenced in a goat model of AF created by Eckstein *et al*. showing an increase in the time of endo-epi dyssynchronous activity during AF (from 17% during acute AF to 68% after 6 months of AF) and in the fractionation of electrograms. They observed a longer effective refractory period (ERP) on the endocardial side in acute AF, however, differences subsided at 6 months [61].

3. COMORBIDITIES AND MARKERS OF DISEASE PROGRESSION PREDICT CATHETER ABLATION OUTCOME

There is considerable data available about the predictors of ablation success in atrial fibrillation that might aid patient selection and ablation strategy (Table **1**). Table **2** shows patient characteristics associated with the good ablation outcomes.

3.1. Lone AF

The apparent lack of predisposing factors is illustrated by an old concept that describes atrial fibrillation without underlying heart disease or traditional risk factors, *i.e*., lone atrial fibrillation [62]. It has been used in a variety of ways in the

Table 1. Predictors of the outcome of AF ablation.

Patient Related Variables	Disease Related Variables	Procedure Related Variables
Age [93]	Persistent AF [143]	High frequency jet ventilation [94]
Valvular heart disease [67]	Duration of AF [66]	Ablation index guided ablation [1]
Hypertension [72]	Extent of low voltage zones [114]	Ablation of triggers elicited with Isoproterenol/Adenosine [95]
OSA [86, 87]	Scar on LGE MRI [115]	Failure to terminate AF during ablation [96]
Obesity [71]	Left atrial appendage asymmetry [79]	Number of procedures [97]
Insulin resistance and diabetes [105, 70]	LA stiffness [122]	Confirmation of entry and exit block [98]
Metabolic syndrome [99]	LA strain [121]	Recurrence in the blanking period [102]
LV dysfunction [68]	LA antero-posterior diameter [113]	-
Ischemic heart disease [100]	LA volume [75,76, 101]	-
Alcohol consumption [92]	PR prolongation [139]	-
Smoking [102]	P wave duration [140]	-
Clinical scores [110-112]	Cycle length of AF [141]	-
-	Dominant frequency of AF [143]	-
-	Extent of areas with CFAE [147]	-

Table 2. Patient characteristics associated with the best AF ablation outcome.

Characteristic	Value/Comment
Age [93]	<65 years
Gender [123]	Male
Paroxysmal AF [65]	HR 3.32 for freedom from arrhythmia after repeat ablation(s)
Duration of persistent AF <6 months [124]	
Absence of comorbidities and structural heart disease – lone AF [102,125]	Success rate after repeat AF ablation(s) as high as 96% [102]
Physical fitness [126]	High cardiorespiratory fitness (>100% predicted METs on treadmill testing)
Weight loss [127]	≥ 10% loss conveys a 6-fold increase of probability of freedom from arrhythmia
Good glycemic control [128]	HbA1c <7% or improvement in HbA1c by >10% during the 1-year preceding ablation
Risk factor management (RFM) [129]*	HR 4.8 for freedom from arrhythmia
CPAP treatment in OSA [130]	Risk of AF recurrence similar to non-OSA patients
LA diameter	<43 mm [131], <41 mm [113]
Left atrial appendage (LAA) flow velocity [132]	>47.7 cm/s
LAVI [77,133]	<34.4 mL/m2
LA volume (CT measurement) [134]	<106 mL
LGE extent	<30% [135], <35% [136]

Note: *RFM included good blood pressure control, weight and lipid management, glycemic control, sleep-disordered breathing management, smoking cessation and reduction of alcohol intake to ▪30 g/week.

literature leading to confusion, but essentially it refers to patients <60 years old without significant coronary artery disease or diabetes who have normal echocardiography, thyroid function tests, and in whom concurrent infection could be excluded [63]. Currently, the concept is being challenged as investigative repertoire to pick up clinical and genetic predisposing factors has improved greatly and groups are advocating for the avoidance of the term altogether [64].

3.2. Predictors of AF Ablation Outcome

It is a well-known fact that more extensive atrial remodeling indicates a worse outcome. Known clinical factors influencing atrial remodeling include type of AF [65], longer duration of AF [66], valvular heart disease [67], cardiomyopathy [68], sleep apnea (OSA) [69], diabetes [70], obesity [71], uncontrolled hypertension [72], *etc*. Surrogate markers of remodeling that predict ablation outcome have been identified as well, such as a more advanced atrial fibrosis on LGE MRI [73] or more extensive low voltage zones (<0.5 mV) with voltage mapping [74], greater LA volume [75, 76] or diameters [77], left atrial asymmetry as evidenced by CT angio in persistent AF patients [78], LA appendage structural remodeling [79], impaired adaptation to the pressure of the LA [80], higher DF of drivers maintaining AF [143], *etc*.

3.3. Duration of AF

The AFA long term registry revealed the real-life situation of AF ablation across Europe with a subanalysis showing that an AF history longer than 2 years resulted in a significantly lower success rate. Although patients with longer duration of AF were older and had more comorbidities, such as ischemic heart disease, hypertension, duration of AF was an independent predictor of AF recurrence [81]. These findings were corroborated by Hussein and colleagues who found that performing catheter ablation after a 3-year history of persistent AF resulted in worse outcomes with multivariable analysis, as was a significantly higher BNP and CRP value and a larger LA diameter, known markers of inflammation and cardiac strain [82]. It is, however, worthwhile remembering that the history of AF may not correlate well with the duration of AF episodes and the extent of atrial remodeling.

3.4. Obstructive Sleep Apnea

Linz *et al*. demonstrated a significantly higher prevalence of OSA in AF patients *vs*. the general population (21% to 74% *vs*. 3% to 49%) [83]. OSA creates episodes of hypoxemia and negative tracheal pressure that, by means of vagal activation, shortens the atrial ERP and increases atrial fibrillation inducibility from 0% at baseline to 90% [84]. OSA related changes to the atrial substrate include lower atrial voltage amplitude, slower conduction velocities, a more extensive electrogram fractionation as well as a higher incidence of extra PV triggers [85], contributing to poorer prognosis of catheter ablation [86, 87].

3.5. Alcohol Consumption

Alcohol consumption is a risk factor that has been shown to alter ionic currents [88], cause oxidative stress [89], and modify cellular metabolism [90], among other effects. Regular moderate alcohol consumption is associated with lower LA conduction velocity and a higher degree of atrial fibrosis [91]. Furthermore, this modifiable risk factor for AF can have an impact on catheter ablation outcomes. Qiao *et al*. reported an increase in AF recurrence with an HR of 1.579 in a population of paroxysmal AF patients, an effect at least party mediated by more extensive left atrial low voltage zones [92].

3.6. Obesity

The effects of obesity have been demonstrated in an animal study published by Meng *et al*., showing that a chronic high-fat diet induces a widening of the atrial interstitial space accompanied by myocyte disarray and downregulation of expression and altered distribution of gap junction proteins, connexin 40 and connexin 43. These changes were in conjuncture with an increase in parameters traditionally associated with fibrosis, namely TGF-β1 and MMP-2 [103]. Okumura *et al*. showed that in pigs, a high fat diet resulted in changes in the electrophysiological characteristics of the atria, such as the shortening of ERP in the pulmonary veins and the superior vena cava (SVC) and an increase in the inducibility and duration of AF [104]. A 2013 meta-analysis confirmed worse catheter ablation outcome in high BMI patients, however, not on multivariate analysis as comorbidities contributed to the effect. Nevertheless, the authors noted a significant improvement in the quality of life in these patients, albeit not due to lesser AF recurrence [71].

3.7. Insulin Resistance

Hijioka *et al*. revealed the role of insulin resistance in the pathogenesis of AF using HOMA-IR (homeostasis model assessment of insulin resistance), a value of ≧ 2.5 independently predicting ablation failure with an HR of 1.287. Of note, patients with insulin resistance did not have a higher left atrial volume index (LAVI) or elevated inflammatory cytokines, such as TNF-α or TGF-β1 levels, yet they exhibited a significantly lower conduction velocity suggesting an effect on the electrophysiological, rather than structural properties of the atria. Patients enrolled in this study had paroxysmal AF and did not have scar areas on voltage maps [105]. Animal studies confirmed that insulin resistance has an impact on AF inducibility [106] and genetically modified type II diabetes rats were shown to have a significantly greater number of repetitive atrial responses as well as longer intra-atrial activation times, but no differences in atrial refractoriness with EP testing [107]. Furthermore, Gu *et al*. demonstrated that thiazolidinediones (peroxisome proliferator-activated receptor (PPAR)-γ agonists), due to their effect on growth factor release, cell proliferation, and migration as well as extracellular matrix remodeling [108], were independent predictors of AF free survival at 12 months (OR= 0.319) [109].

3.8. Clinical Scores for Prediction of AF Ablation Outcome

Several scores for predicting AF ablation outcomes have been published incorporating known risk factors for AF progression and atrial remodeling. LAGO (AF phenotype, struc-

tural heart disease, CHA2DS2-VASc ≤ 1, LA diameter, and LA sphericity) predicted poor ablation outcome with HR of 3.10 at 3 years [110]. In a study published by Potpara *et al*., the MB-LATER score (1 point for male gender, bundle branch block, left atrial diameter ≥47 mm, persistent AF and early recurrence of AF during blanking, 2 points for the pre-ablation history of long-standing persistent AF) significantly predicted late recurrence of AF; however, its predictive accuracy was poor (AUC 0.62) and none of the other tested predictive scores (CAAP-AF, CHA2DS2-VASc, and CHADS2) yielded better results in this patient population [111]. In contrast, in a population of paroxysmal AF patients, Chao *et al*. demonstrated that the CHADS2 scores, along with left atrial diameter, were significant predictors of recurrent AF and identified patients with low (2.9%, with CHADS2 0 score) and high recurrence rates (63.6% with CHADS2 score ≥3) at 2 years [112].

3.9. Echocardiography Parameters

Information about left atrial structural changes can be gained non-invasively and at low cost with echocardiography. Motoc *et al*. evaluated LA anteroposterior diameter (LAD) and LA minimum volume (LAmin) in paroxysmal patients, and found that cut offs of 41 mm and 23.69 mL, respectively, had a fair predictive value for recurrence of AF after catheter ablation (negative predictive values of 73% and 87.3%). Interestingly, 30% of the patients with recurrence had a LAD within the normal range, however, they exhibited remodeling in the infero-posterior axis (longitudinal remodeling) [113].

3.10. Atrial Scarring

There is consensus regarding the fact that extensive low voltage areas (LVA) (<0.5 mV) are associated with poorer ablation success [114]. Scar tissue can also be quantified using MRI, a non-invasive and well-studied imaging modality. Chelu and colleagues published a study in which LGE MRI was performed in patients ablated for AF (which included a posterior wall debulking in 90% of patients) and showed that during a 5-year follow-up, the degree of atrial fibrosis (Utah stage IV *versus* stage I) was independently associated with arrhythmia recurrence with an HR of 2.73. All patients with Utah stage IV atrial fibrosis experienced recurrent AF after ablation at 5 years [115]. Whether or not performing substrate modification, in addition to PVI will improve outcome is a subject of debate. The STAR-AF trial conducted by Verma *et al*. did not show any benefit if linear ablation or ablation of complex fractionated electrograms (CFAE) were performed in addition to pulmonary-vein isolation [116], however, several authors reported higher freedom from AF [117, 118] including a 2017 meta-analysis [119].

3.11. Remodeling of the Left Appendage

Suksaranjit and colleagues described a similar impact of left atrial appendage structural remodeling (demonstrated by LGE on MRI) on the success of catheter ablation, patients in the highest tier, or LAA fibrosis experiencing 73.3% AF recurrence *versus* 37.5% in patients in the lowest tier [79]. Although empirical isolation of the left atrial appendage would seem to be an obvious resolve, it has been shown to predispose to thrombus formation and stroke [120].

3.12. Left Atrial Function and Stiffness Index

Left atrial function can be assessed by measuring LA systolic strain, which has been shown to be reduced in patients with AF and especially in those with AF recurrences after catheter ablation. Yasuda *et al*. compared left atrial global strain, LA lateral total strain, as well as LAVI max, in patients with and without recurrence and found LA lateral strain to be a significant predictor or AF recurrence with an AUC 0.84, outperforming LAVImax (having an AUC of 0.74 and unable to predict the unfavorable outcome if the patient was in sinus rhythm during the echocardiographic measurements) [121].

Khurram *et al*. introduced the term stiffness index (SI) to describe the impaired adaptation of the left atrium to changes in loading conditions. It is defined as the ratio of the change in left atrial pressure to the change in left atrial volume during the passive filling of the LA. The index was higher in persistent AF, older age, in patients with previous ablation(s) and in patients with AF recurrences after catheter ablation, with a recurrence rate of 5% in the lower quartile compared to 59% in the highest quartile [122].

3.13. Predictors Derived from the Surface ECG

The surface ECG in sinus rhythm can be revealing as well; PR prolongation, a mark of atrial and atrioventricular conduction slowing has been shown to predict the development of AF [137] and was associated with the presence of left atrial low voltage areas [138], older age, the persistent form of AF, larger LA dimensions, and higher LAVI. It was also a significant predictor of the outcome of catheter ablation (HR=1.969, 95% CI 1.343 to 2.886, P=0.001) [139]. These results were reiterated by Hu *et al*., who measured P wave duration (PWD) and the difference between pre- and post-procedural values (PWD variation). They found that AF ablation shortened PWD in the inferior leads, V1 and a lesser shortening was associated with an unfavorable AF ablation outcome (PWD variation ≥-2.21 ms in lead II had a sensitivity and specificity of 85.29% and 83.94%, respectively; AUC of 0.868) [140].

3.14. Characteristics of Fibrillatory Activity

There are insights to be gained from the characterization of the fibrillatory activity during AF either based on the surface ECG or intracardiac electrograms that might indicate the complexity of the atrial substrate and the prospective outcome of AF ablation. Predictors of the success of catheter ablation can be derived from the time- and frequency domain of fibrillatory activity of the atria indicative of electrical remodeling, high dominant frequency (DF) sites representing either focal sources or re-entries. A shorter cycle length [141], a higher dominant frequency, and a decreased level of organization of AF [142-144] were shown to predict poor outcomes. A lower ablation success was noted in patients with higher RA dominant frequency and lower CSd to RA DF gradient, indicating the presence of a RA source not targeted by PV isolation and LA ablation [143]. Of note, no

pre-procedural surface ECG spectral parameter has been found that is easy-to-use and could reliably guide patient selection.

Do CFAEs arise at driver sites or are they merely the result of wavefront collision, and if so, what is the value of their ablation? Some argue they are pivot points, areas of local re-entry and slow conduction and are responsible for the maintenance of AF [145, 146]. It is known that the percent area of CFAE is larger and the mean CL of the CFAE is shorter in patients with a more remodeled LA [147]. The STAR-AF II and CHASE-AF trials did not demonstrate any added benefit to PVI with CFAE ablation [116, 148], and a recent meta-analysis showed that performing additional CFAE ablation increased ablation success only in persistent AF patients, albeit with a rise in procedure time, fluoroscopy time as well as post-procedural ATs [149].

3.15. Reverse Remodeling

There is evidence suggesting the reversal of remodeling after catheter ablation. Fujimoto found that a decrease in P-wave dispersion, a marker of prolonged and inhomogeneous impulse conduction starting from 3 months post-ablation, indicates the favorable outcome and reverse remodeling along with the decrease of left atrial size and BNP level. They also noted that the latency in the decrease suggests that the maintenance of sinus rhythm might be largely responsible for it [150]. A subgroup analysis of the CAMERA-MRI study showed a significant increase in the RA myocardial voltage especially at the posterior and septal segments as well as a significant decrease in complex fractionated electrograms besides improvements in LV function and LA area in heart failure patients who remained in SR >90% of the time after catheter ablation [151]. In an elegant study, however, Teh *et al*. demonstrated further progression in terms of decrease in bipolar voltage, lengthening of the ERP, slowing of the conduction velocity as well as an increase in the proportion of complex signals despite a significant decrease in left atrial size. Interestingly, despite no AF reported during the follow-up, AF was inducible in the EP lab in 5/11 patients, three requiring cardioversion for AF lasting >60 minutes [152].

CONCLUSION

There is excellent basic science available on the pathophysiology of AF, including changes in molecular biology, histology, ionic channel remodeling, as well as computational models that demonstrate the arrhythmogenicity of fibrosis. Understanding the mechanism of AF initiation and maintenance, and the profound and multifaceted effect risk factors have on the structure and function of the atrial myocardium is key in developing more effective treatments.

It is important to identify patients at risk of developing AF and manage factors that contribute to disease progression and have an impact on ablation success. It will help patient selection and planning of the procedure – more extensive ablation for more remodeled atria as well as managing patient expectations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Taghji P, El Haddad M, Phlips T, *et al.* Evaluation of a Strategy Aiming to Enclose the Pulmonary Veins With Contiguous and Optimized Radiofrequency Lesions in Paroxysmal Atrial Fibrillation: A Pilot Study. JACC Clin Electrophysiol 2018; 4(1): 99-108. http://dx.doi.org/10.1016/j.jacep.2017.06.023 PMID: 29600792

[2] Ganesan AN, Shipp NJ, Brooks AG, *et al.* Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013; 2(2): e004549. http://dx.doi.org/10.1161/JAHA.112.004549 PMID: 23537812

[3] Verma A, Macle L. Persistent atrial fibrillation ablation: where do we go from here? Can J Cardiol 2018; 34(11): 1471-81. http://dx.doi.org/10.1016/j.cjca.2018.08.008 PMID: 30404751

[4] Tutuianu C, Szilagy J, Pap R, Sághy L. Very long-term results of atrial fibrillation ablation confirm that this therapy is really effective. J Atr Fibrillation 2015; 8(2): 1226. http://dx.doi.org/10.4022/jafib.1226 PMID: 27957186

[5] Szilágyi J, Marcus GM, Badhwar N, *et al.* Atrial fibrillation patients with isolated pulmonary veins: Is sinus rhythm achievable? J Cardiovasc Electrophysiol 2017; 28(7): 754-61. http://dx.doi.org/10.1111/jce.13230 PMID: 28429499

[6] Sadek MM, Maeda S, Chik W, *et al.* Recurrent atrial arrhythmias in the setting of chronic pulmonary vein isolation. Heart Rhythm 2016; 13(11): 2174-80. http://dx.doi.org/10.1016/j.hrthm.2016.08.026 PMID: 27544746

[7] Tanaka K, Zlochiver S, Vikstrom KL, *et al.* Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ Res 2007; 101(8): 839-47. http://dx.doi.org/10.1161/CIRCRESAHA.107.153858 PMID: 17704207

[8] Benito EM, Cabanelas N, Nuñez-Garcia M, *et al.* Preferential regional distribution of atrial fibrosis in posterior wall around left inferior pulmonary vein as identified by late gadolinium enhancement cardiac magnetic resonance in patients with atrial fibrillation. Europace 2018; 20(12): 1959-65. http://dx.doi.org/10.1093/europace/euy095 PMID: 29860416

[9] Saba S, Janczewski AM, Baker LC, *et al.* Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-alpha. Am J Physiol Heart Circ Physiol 2005; 289(4): H1456-67. http://dx.doi.org/10.1152/ajpheart.00733.2004 PMID: 15923312

[10] Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015; 12(4): 230-43. http://dx.doi.org/10.1038/nrcardio.2015.2 PMID: 25622848

[11] Gertz ZM, Raina A, Saghy L, *et al.* Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. J Am Coll Cardiol 2011; 58(14): 1474-81. http://dx.doi.org/10.1016/j.jacc.2011.06.032 PMID: 21939832

[12] Al Chekakie MO, Welles CC, Metoyer R, *et al.* Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol 2010; 56(10): 784-8. http://dx.doi.org/10.1016/j.jacc.2010.03.071 PMID: 20797492

[13] Tsao HM, Hu WC, Wu MH, *et al.* Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left

atrium in patients with atrial fibrillation and effect of recurrence after ablation. Am J Cardiol 2011; 107(10): 1498-503. http://dx.doi.org/10.1016/j.amjcard.2011.01.027 PMID: 21414593

[14] Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997; 96(4): 1180-1184. http://dx.doi.org/10.1161/01.CIR.96.4.1180

[15] Oishi S, Sasano T, Tateishi Y, Tamura N, Isobe M, Furukawa T. Stretch of atrial myocytes stimulates recruitment of macrophages *via* ATP released through gap-junction channels. J Pharmacol Sci 2012; 120(4): 296-304. http://dx.doi.org/10.1254/jphs.12202fp

[16] Sun Z, Zhou D, Xie X, *et al.* Cross-talk between macrophages and atrial myocytes in atrial fibrillation. Basic Res Cardiol 2016; 111(6): 63. http://dx.doi.org/10.1007/s00395-016-0584-z PMID: 27660282

[17] Nattel S. Molecular and cellular mechanisms of atrial fibrosis in atrial fibrillation. JACC Clin Electrophysiol 2017; 3(5): 425-35. http://dx.doi.org/10.1016/j.jacep.2017.03.002 PMID: 29759598

[18] Corradi D, Callegari S, Benussi S, *et al.* Myocyte changes and their left atrial distribution in patients with chronic atrial fibrillation related to mitral valve disease. Hum Pathol 2005; 36(10): 1080-9. http://dx.doi.org/10.1016/j.humpath.2005.07.018 PMID: 16226107

[19] Duprez DA, Heckbert SR, Alonso A, *et al.* Collagen biomarkers and incidence of new onset of atrial fibrillation in subjects with no overt cardiovascular disease at baseline: The multi-ethnic study of atherosclerosis. Circ Arrhythm Electrophysiol 2018; 11(10): e006557. http://dx.doi.org/10.1161/CIRCEP.118.006557 PMID: 30354407

[20] Zipes D, Jalife J. Cardiac electrophysiology: from cell to bedside. 6th edition. © Saunders 2013; pp. 459-465.

[21] Rook MB, van Ginneken AC, de Jonge B, el Aoumari A, Gros D, Jongsma HJ. Differences in gap junction channels between cardiac myocytes, fibroblasts, and heterologous pairs. Am J Physiol 1992; 263(5 Pt 1): C959-77. http://dx.doi.org/10.1152/ajpcell.1992.263.5.C959 PMID: 1279981

[22] Zlochiver S, Muñoz V, Vikstrom KL, Taffet SM, Berenfeld O, Jalife J. Electrotonic myofibroblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers. Biophys J 2008; 95(9): 4469-80. http://dx.doi.org/10.1529/biophysj.108.136473 PMID: 18658226

[23] Jansen JA, van Veen TA, de Bakker JM, van Rijen HV. Cardiac connexins and impulse propagation. J Mol Cell Cardiol 2010; 48(1): 76-82. http://dx.doi.org/10.1016/j.yjmcc.2009.08.018 PMID: 19729017

[24] van der Velden HM, Ausma J, Rook MB, *et al.* Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. Cardiovasc Res 2000; 46(3): 476-86. http://dx.doi.org/10.1016/S0008-6363(00)00026-2 PMID: 10912458

[25] Myerburg RJ, Nilsson K, Befeler B, Castellanos A Jr, Gelband H. Transverse spread and longitudinal dissociation in the distal A-V conducting system. J Clin Invest 1973; 52(4): 885-95. http://dx.doi.org/10.1172/JCI107253 PMID: 4693653

[26] Allessie MA, de Groot NMS, Houben RPM, *et al.* Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. Circ Arrhythm Electrophysiol 2010; 3(6): 606-15. http://dx.doi.org/10.1161/CIRCEP.109.910125 PMID: 20719881

[27] Haemers P, Hamdi H, Guedj K, *et al.* Atrial fibrillation is associated with the fibrotic remodelling of adipose tissue in the subepicardium of human and sheep atria. Eur Heart J 2017; 38(1): 53-61. http://dx.doi.org/10.1093/eurheartj/ehv625 PMID: 26612579

[28] Venteclef N, Guglielmi V, Balse E, *et al.* Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J 2015; 36(13): 795-805a. http://dx.doi.org/10.1093/eurheartj/eht099 PMID: 23525094

[29] Voigt N, Li N, Wang Q, *et al.* Enhanced sarcoplasmic reticulum Ca^{2+} leak and increased Na^{+}-Ca^{2+} exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. Circulation 2012; 125(17): 2059-70. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.067306 PMID: 22456474

[30] Hove-Madsen L, Llach A, Bayes-Genís A, *et al.* Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. Circulation 2004; 110(11): 1358-63. http://dx.doi.org/10.1161/01.CIR.0000141296.59876.87 PMID: 15313939

[31] Li N, Chiang DY, Wang S, *et al.* Ryanodine receptor-mediated calcium leak drives progressive development of an atrial fibrillation substrate in a transgenic mouse model. Circulation 2014; 129(12): 1276-85. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.006611 PMID: 24398018

[32] Sumitomo N, Sakurada H, Taniguchi K, *et al.* Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. Circ J 2007; 71(10): 1606-9. http://dx.doi.org/10.1253/circj.71.1606 PMID: 17895559

[33] Forte M, Nocella C, De Falco E, *et al.* The pathophysiological role of NOX2 in hypertension and organ damage. High Blood Press Cardiovasc Prev 2016; 23(4): 355-64. http://dx.doi.org/10.1007/s40292-016-0175-y PMID: 27915400

[34] Liu T, Shao Q, Korantzopoulos P, Liu E, Xu G, Li G. Serum levels of nicotinamide-adenine dinucleotide phosphate oxidase 4 are associated with non-valvular atrial fibrillation. Biomed Rep 2015; 3(6): 864-8. http://dx.doi.org/10.3892/br.2015.504 PMID: 26623031

[35] Reilly SN, Jayaram R, Nahar K, *et al.* Atrial sources of reactive oxygen species vary with the duration and substrate of atrial fibrillation: implications for the antiarrhythmic effect of statins. Circulation 2011; 124(10): 1107-17. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.029223 PMID: 21844076

[36] Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. Trends Cardiovasc Med 2015; 25(6): 475-84. http://dx.doi.org/10.1016/j.tcm.2014.12.015 PMID: 25661032

[37] Xie W, Santulli G, Reiken SR, *et al.* Mitochondrial oxidative stress promotes atrial fibrillation. Sci Rep 2015; 5: 11427. http://dx.doi.org/10.1038/srep11427 PMID: 26169582

[38] Catalucci D, Latronico MV, Condorelli G. MicroRNAs control gene expression: importance for cardiac development and pathophysiology. Ann N Y Acad Sci 2008; 1123: 20-9. http://dx.doi.org/10.1196/annals.1420.004 PMID: 18375574

[39] Wang Z, Lu Y, Yang B. MicroRNAs and atrial fibrillation: new fundamentals. Cardiovasc Res 2011; 89(4): 710-21. http://dx.doi.org/10.1093/cvr/cvq350 PMID: 21051420

[40] Linz D, Elliott AD, Hohl M, *et al.* Role of autonomic nervous system in atrial fibrillation. Int J Cardiol 2019; 287: 181-8. http://dx.doi.org/10.1016/j.ijcard.2018.11.091

[41] Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev 2011; 91(1): 265-325. http://dx.doi.org/10.1152/physrev.00031.2009

[42] van den Berg MP, Hassink RJ, Tuinenburg AE, *et al.* Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. Eur Heart J 2001; 22(3): 247-53. http://dx.doi.org/10.1053/euhj.2001.2180 PMID: 11161936

[43] Ando SI. Influence of hypoxia induced by sleep disordered breathing in case of hypertension and atrial fibrillation. J Cardiol 2018; 72(1): 10-18. http://dx.doi.org/10.1016/j.jjcc.2018.02.016

[44] Linz D, van Hunnik A, Hohl M, *et al.* Catheter-based renal denervation reduces atrial nerve sprouting and complexity of atrial fibrillation in goats. Circ Arrhythm Electrophysiol 2015; 8(2): 466-74. http://dx.doi.org/10.1161/CIRCEP.114.002453 PMID: 25713217

[45] Katritsis DG, Pokushalov E, Romanov A, *et al.* Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol 2013; 62(24): 2318-2325. http://dx.doi.org/10.1016/j.jacc.2013.06.053

[46] Dobrev D, Graf E, Wettwer E, *et al.* Molecular basis of downregulation of G-protein-coupled inward rectifying $K^{(+)}$ current (I(K,ACh) in chronic human atrial fibrillation: decrease in GIRK4 mRNA correlates with reduced I(K,ACh) and muscarinic receptor-mediated shortening of action potentials. Circulation 2001; 104(21): 2551-7. http://dx.doi.org/10.1161/hc4601.099466 PMID: 11714649

[47] Martins RP, Kaur K, Hwang E, *et al.* Dominant frequency increase rate predicts transition from paroxysmal to long-term persistent atrial fibrillation. Circulation 2014; 129(14): 1472-82. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.004742 PMID: 24463369

[48] Chen YH, Xu SJ, Bendahhou S, *et al.* KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science 2003; 299(5604): 251-4. http://dx.doi.org/10.1126/science.1077771 PMID: 12522251

[49] Lieve KV, Verkerk AO, Podliesna S, *et al.* Gain-of-function mutation in SCN5A causes ventricular arrhythmias and early onset atrial fibrillation. Int J Cardiol 2017; 236: 187-93. http://dx.doi.org/10.1016/j.ijcard.2017.01.113 PMID: 28262340

[50] Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J Cardiovasc Electrophysiol 2005; 16(4): 394-6. http://dx.doi.org/10.1046/j.1540-8167.2005.40621.x PMID: 15828882

[51] Fatini C, Sticchi E, Genuardi M, *et al.* Analysis of minK and eNOS genes as candidate loci for predisposition to non-valvular atrial fibrillation. Eur Heart J 2006; 27(14): 1712-8. http://dx.doi.org/10.1093/eurheartj/ehl087 PMID: 16760206

[52] Elvan A, Rubart M, Zipes DP. NO modulates autonomic effects on sinus discharge rate and AV nodal conduction in open-chest dogs. Am J Physiol 1997; 272(1 Pt 2): H263-71. PMID: 9038946

[53] Méry PF, Pavoine C, Belhassen L, Pecker F, Fischmeister R. Nitric oxide regulates cardiac Ca^{2+} current. Involvement of cGMP-inhibited and cGMP-stimulated phosphodiesterases through guanylyl cyclase activation. J Biol Chem 1993; 268(35): 26286-95. PMID: 7902837

[54] Holm H, Gudbjartsson DF, Arnar DO, *et al.* Several common variants modulate heart rate, PR interval and QRS duration. Nat Genet 2010; 42(2): 117-22. http://dx.doi.org/10.1038/ng.511 PMID: 20062063

[55] Pfeufer A, van Noord C, Marciante KD, *et al.* Genome-wide association study of PR interval. Nat Genet 2010; 42(2): 153-9. http://dx.doi.org/10.1038/ng.517 PMID: 20062060

[56] Sano M, Kamitsuji S, Kamatani N, *et al.* Japan Pharmacogenomics Data Science Consortium (JPDSC). Genome-wide association study of electrocardiographic parameters identifies a new association for PR interval and confirms previously reported associations. Hum Mol Genet 2014; 23(24): 6668-76. http://dx.doi.org/10.1093/hmg/ddu375 PMID: 25055868

[57] Butler AM, Yin X, Evans DS, *et al.* Novel loci associated with PR interval in a genome-wide association study of 10 African American cohorts. Circ Cardiovasc Genet 2012; 5(6): 639-46. http://dx.doi.org/10.1161/CIRCGENETICS.112.963991 PMID: 23139255

[58] Ikeda T, Zhang J, Chano T, *et al.* Identification and characterization of the human long form of Sox5 (L-SOX5) gene. Gene 2002; 298(1): 59-68. http://dx.doi.org/10.1016/S0378-1119(02)00927-7 PMID: 12406576

[59] de Groot N, van der Does L, Yaksh A, *et al.* Direct proof of endo-epicardial asynchrony of the atrial wall during atrial fibrillation in humans. Circ Arrhythm Electrophysiol 2016; 9(5): e003648. http://dx.doi.org/10.1161/CIRCEP.115.003648 PMID: 27103089

[60] Hansen BJ, Zhao J, Csepe TA, *et al.* Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J 2015; 36(35): 2390-401. http://dx.doi.org/10.1093/eurheartj/ehv233 PMID: 26059724

[61] Eckstein J, Maesen B, Linz D, *et al.* Time course and mechanisms of endo-epicardial electrical dissociation during atrial fibrillation in the goat. Cardiovasc Res 2011; 89(4): 816-24. http://dx.doi.org/10.1093/cvr/cvq336 PMID: 20978006

[62] Evans W, Swann P. Lone auricular fibrillation. Br Heart J 1954; 16(2): 189-94. http://dx.doi.org/10.1136/hrt.16.2.189 PMID: 13160271

[63] Wyse DG, Van Gelder IC, Ellinor PT, *et al.* Lone atrial fibrillation. J Am Coll Cardiol 2014; 63(17): 1715-23. http://dx.doi.org/10.1016/j.jacc.2014.01.023

[64] Wyse DG, Van Gelder IC, Ellinor PT, *et al.* Lone atrial fibrillation: does it exist? J Am Coll Cardiol 2014; 63(17): 1715-23. http://dx.doi.org/10.1016/j.jacc.2014.01.023 PMID: 24530673

[65] Bhargava M, Di Biase L, Mohanty P, *et al.* Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. Heart Rhythm 2009; 6(10): 1403-12. http://dx.doi.org/10.1016/j.hrthm.2009.06.014 PMID: 19716348

[66] Takigawa M, Takahashi A, Kuwahara T, *et al.* Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. Circ Arrhythm Electrophysiol 2014; 7(2): 267-73. http://dx.doi.org/10.1161/CIRCEP.113.000471 PMID: 24610740

[67] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82(8A): 2N-9N. http://dx.doi.org/10.1016/S0002-9149(98)00583-9 PMID: 9809895

[68] Weerasooriya R, Khairy P, Litalien J, *et al.* Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011; 57(2): 160-6. http://dx.doi.org/10.1016/j.jacc.2010.05.061 PMID: 21211687

[69] Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. Coron Artery Dis 1996; 7(6): 475-8. http://dx.doi.org/10.1097/00019501-199606000-00011 PMID: 8889364

[70] Dublin S, Glazer NL, Smith NL, *et al.* Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med 2010; 25(8): 853-8. http://dx.doi.org/10.1007/s11606-010-1340-y PMID: 20405332

[71] Zhuang J, Lu Y, Tang K, Peng W, Xu Y. Influence of body mass index on recurrence and quality of life in atrial fibrillation patients after catheter ablation: a meta-analysis and systematic review. Clin Cardiol 2013; 36(5): 269-75. http://dx.doi.org/10.1002/clc.22108 PMID: 23494488

[72] Kamioka M, Hijioka N, Matsumoto Y, *et al.* Uncontrolled blood pressure affects atrial remodeling and adverse clinical outcome in paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2018; 41(4): 402-10. http://dx.doi.org/10.1111/pace.13311 PMID: 29446840

[73] Marrouche NF, Wilber D, Hindricks G, *et al.* Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014; 311(5): 498-506. http://dx.doi.org/10.1001/jama.2014.3 PMID: 24496537

[74] Masuda M, Fujita M, Iida O, *et al.* Left atrial low-voltage areas predict atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. Int J Cardiol 2018; 257: 97-101. http://dx.doi.org/10.1016/j.ijcard.2017.12.089 PMID: 29506746

[75] Kohári M, Zado E, Marchlinski FE, Callans DJ, Han Y. Left atrial volume best predicts recurrence after catheter ablation in patients with persistent and longstanding persistent atrial fibrillation. Pacing Clin Electrophysiol 2014; 37(4): 422-9. http://dx.doi.org/10.1111/pace.12279 PMID: 24164571

[76] Celik AI, Kanadasi M, Demir M, *et al.* Predictors of the paroxysmal atrial fibrillation recurrence following cryoballoon-based pulmonary vein isolation: Assessment of left atrial volume, left atrial volume index, galectin-3 level and neutrophil-to-lymphocyte ratio. Indian Pacing Electrophysiol J 2019; 19(1): 9-14. http://dx.doi.org/10.1016/j.ipej.2018.07.003 PMID: 30712532

[77] Zhuang J, Wang Y, Tang K, *et al.* Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace 2012; 14(5): 638-45. http://dx.doi.org/10.1093/europace/eur364 PMID: 22117033

[78] Nedios S, Koutalas E, Sommer P, *et al.* Asymmetrical left atrial remodelling in atrial fibrillation: relation with diastolic dysfunction and long-term ablation outcomes. Europace 2017; 19(9): 1463-9. http://dx.doi.org/10.1093/europace/euw225 PMID: 27738076

[79] Suksaranjit P, Marrouche NF, Han FT, *et al.* Relation of Left Atrial Appendage Remodeling by Magnetic Resonance Imaging and Outcome of Ablation for Atrial Fibrillation. Am J Cardiol 2018; 122(1): 83-8. http://dx.doi.org/10.1016/j.amjcard.2018.03.027 PMID: 29731119

[80] Ágoston G, Szilágyi J, Bencsik G, *et al.* Impaired adaptation to left atrial pressure increase in patients with atrial fibrillation. J Interv Card Electrophysiol 2015; 44(2): 113-8. http://dx.doi.org/10.1007/s10840-015-0032-2 PMID: 26123096

[81] Stabile G, Trines SA, Arbelo E, *et al.* ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry investigators. Atrial fibrillation history impact on catheter ablation outcome. Findings from the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry. Pacing Clin Electrophysiol 2019; 42(3): 313-20. http://dx.doi.org/10.1111/pace.13600 PMID: 30632196

[82] Hussein AA, Saliba WI, Barakat A, *et al.* Radiofrequency Ablation of Persistent Atrial Fibrillation: Diagnosis-to-Ablation Time, Markers of Pathways of Atrial Remodeling, and Outcomes. Circ Arrhythm Electrophysiol 2016; 9(1): e003669. http://dx.doi.org/10.1161/CIRCEP.115.003669 PMID: 26763227

[83] Linz D, McEvoy RD, Cowie MR, *et al.* Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: A review. JAMA Cardiol 2018; 3(6): 532-40. http://dx.doi.org/10.1001/jamacardio.2018.0095 PMID: 29541763

[84] Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. Heart Rhythm 2011; 8(9): 1436-43. http://dx.doi.org/10.1016/j.hrthm.2011.03.053 PMID: 21457790

[85] Anter E, Di Biase L, Contreras-Valdes FM, *et al.* Atrial substrate and triggers of paroxysmal atrial fibrillation in patients with obstructive sleep apnea. Circ Arrhythm Electrophysiol 2017; 10(11): e005407. http://dx.doi.org/10.1161/CIRCEP.117.005407 PMID: 29133380

[86] Jongnarangsin K, Chugh A, Good E, *et al.* Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2008; 19: 668-72.

[87] Matiello M, Nadal M, Tamborero D, *et al.* Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients. Europace 2010; 12(8): 1084-9. http://dx.doi.org/10.1093/europace/euq128 PMID: 20488856

[88] Ettinger PO, Lyons M, Oldewurtel HA, Regan TJ. Cardiac conduction abnormalities produced by chronic alcoholism. Am Heart J 1976; 91(1): 66-78. http://dx.doi.org/10.1016/S0002-8703(76)80436-X PMID: 942675

[89] Piano MR, Phillips SA. Alcoholic cardiomyopathy: pathophysiologic insights. Cardiovasc Toxicol 2014; 14(4): 291-308. http://dx.doi.org/10.1007/s12012-014-9252-4 PMID: 24671642

[90] Piano MR. Alcohol's effects on the cardiovascular system. Alcohol Res 2017; 38(2): 219-41. PMID: 28988575

[91] Voskoboinik A, Wong G, Lee G, *et al.* Moderate alcohol consumption is associated with atrial electrical and structural changes: Insights from high-density left atrial electroanatomic mapping. Heart Rhythm 2019; 16(2): 251-9. http://dx.doi.org/10.1016/j.hrthm.2018.10.041 PMID: 30639070

[92] Qiao Y, Shi R, Hou B, *et al.* Impact of alcohol consumption on substrate remodeling and ablation outcome of paroxysmal atrial fibrillation. J Am Heart Assoc 2015; 4(11): e002349. http://dx.doi.org/10.1161/JAHA.115.002349 PMID: 26553213

[93] Lee SH, Tai CT, Hsieh MH, *et al.* Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. J Interv Card Electrophysiol 2004; 10(3): 221-6. http://dx.doi.org/10.1023/B:JICE.0000026915.02503.92

[94] Sivasambu B, Hakim JB, Barodka V, *et al.* Initiation of a high-frequency jet ventilation strategy for catheter ablation for atrial fibrillation: safety and outcomes data. JACC Clin Electrophysiol 2018; 4(12): 1519-25. http://dx.doi.org/10.1016/j.jacep.2018.08.016

[95] Lin D, Frankel DS, Zado ES, *et al.* Pulmonary vein antral isolation and nonpulmonary vein trigger ablation without additional substrate modification for treating longstanding persistent atrial fibrillation. J Cardiovasc Electrophysiol 2012; 23(8): 806-13. http://dx.doi.org/10.1111/j.1540-8167.2012.02307.x PMID: 22509772

[96] Scherr D, Khairy P, Miyazaki S, *et al.* Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. Circ Arrhythm Electrophysiol 2015; 8(1): 18-24. http://dx.doi.org/10.1161/CIRCEP.114.001943

[97] Schreiber D, Rostock T, Fröhlich M, *et al.* Five-year follow-up after catheter ablation of persistent atrial fibrillation using the stepwise approach and prognostic factors for success. Circ Arrhythm Electrophysiol 2015; 8(2): 308-17.

[98] Bertaglia E, Stabile G, Senatore G, *et al.* Documentation of pulmonary vein isolation improves long term efficacy of persistent atrial fibrillation catheter ablation. Int J Cardiol 2014; 171(2): 174-8. http://dx.doi.org/10.1016/j.ijcard.2013.11.055

[99] Mohanty S, Mohanty P, Di Biase L, *et al.* Impact of metabolic syndrome on procedural outcomes in patients with atrial fibrillation undergoing catheter ablation. J Am Coll Cardiol 2012; 59(14): 1295-301. http://dx.doi.org/10.1016/j.jacc.2011.11.051 PMID: 22464257

[100] Hiraya D, Sato A, Hoshi T, *et al.* Impact of coronary artery disease and revascularization on recurrence of atrial fibrillation after catheter ablation: Importance of ischemia in managing atrial fibrillation. J Cardiovasc Electrophysiol 2019; 30(9): 1491-8. http://dx.doi.org/10.1111/jce.14029

[101] Njoku A, Kannabhiran M, Arora R, *et al.* Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. Europace 2018; 20(1): 33-42. http://dx.doi.org/10.1093/europace/eux013

[102] Buiatti A, Kaess B, Reents T, *et al.* Catheter ablation for "Lone" atrial fibrillation: Efficacy and predictors of recurrence. J Cardiovasc Electrophysiol 2016; 27(5): 536-41. http://dx.doi.org/10.1111/jce.12936

[103] Meng T, Cheng G, Wei Y, *et al.* Exposure to a chronic high-fat diet promotes atrial structure and gap junction remodeling in rats. Int J Mol Med 2017; 40(1): 217-25. http://dx.doi.org/10.3892/ijmm.2017.2982 PMID: 28498436

[104] Okumura Y, Watanabe I, Nagashima K, *et al.* Effects of a high-fat diet on the electrical properties of porcine atria. J Arrhythm 2015; 31(6): 352-8. http://dx.doi.org/10.1016/j.joa.2015.05.004 PMID: 26702314

[105] Hijioka N, Kamioka M, Matsumoto Y, *et al.* Clinical impact of insulin resistance on pulmonary vein isolation outcome in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2019; 30(4): 479-86. http://dx.doi.org/10.1111/jce.13827 PMID: 30575179

[106] Maria Z, Campolo AR, Scherlag BJ, Ritchey JW, Lacombe VA. Dysregulation of insulin-sensitive glucose transporters during insulin resistance-induced atrial fibrillation. Biochim Biophys Acta Mol Basis Dis 2018; 1864(4 Pt A): 987-96. http://dx.doi.org/10.1016/j.bbadis.2017.12.038 PMID: 29291943

[107] Kato T, Yamashita T, Sekiguchi A, *et al.* What are arrhythmogenic substrates in diabetic rat atria? J Cardiovasc Electrophysiol 2006; 17(8): 890-4. http://dx.doi.org/10.1111/j.1540-8167.2006.00528.x PMID: 16759295

[108] Giannini S, Serio M, Galli A. Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic activity. J Endocrinol Invest 2004; 27(10): 982-91. http://dx.doi.org/10.1007/BF03347546 PMID: 15762051

[109] Gu J, Liu X, Wang X, *et al.* Beneficial effect of pioglitazone on the outcome of catheter ablation in patients with paroxysmal atrial fibrillation and type 2 diabetes mellitus. Europace 2011; 13(9): 1256-61. http://dx.doi.org/10.1093/europace/eur131 PMID: 21551479

[110] Bisbal F, Alarcón F, Ferrero-de-Loma-Osorio A, *et al.* Left atrial geometry and outcome of atrial fibrillation ablation: results from the multicentre LAGO-AF study. Eur Heart J Cardiovasc Imaging 2018; 19(9): 1002-9. http://dx.doi.org/10.1093/ehjci/jey060 PMID: 29659784

[111] Potpara TS, Mujovic N, Sivasambu B, *et al.* Validation of the MB-LATER score for prediction of late recurrence after catheter-ablation of atrial fibrillation. Int J Cardiol 2019; 276: 130-5. http://dx.doi.org/10.1016/j.ijcard.2018.08.018 PMID: 30126656

[112] Chao TF, Ambrose K, Tsao HM, *et al.* Relationship between the CHADS(2) score and risk of very late recurrences after catheter ablation of paroxysmal atrial fibrillation. Heart Rhythm 2012; 9(8): 1185-91. http://dx.doi.org/10.1016/j.hrthm.2012.03.007 PMID: 22406145

[113] Motoc A, Abugattas JP, Roosens B, *et al.* Left atrium remodeling predicts late recurrence of paroxysmal atrial fibrillation after second generation cryoballoon ablation. Cardiovasc Ultrasound 2018; 16(1): 19. http://dx.doi.org/10.1186/s12947-018-0137-8 PMID: 30249263

[114] Verma A, Wazni OM, Marrouche NF, *et al.* Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation:

an independent predictor of procedural failure. J Am Coll Cardiol 2005; 45(2): 285-92.
http://dx.doi.org/10.1016/j.jacc.2004.10.035 PMID: 15653029

[115] Chelu MG, King JB, Kholmovski EG, *et al.* Atrial fibrosis by late gadolinium enhancement magnetic resonance imaging and catheter ablation of atrial fibrillation: 5-year follow-up data. J Am Heart Assoc 2018; 7(23): e006313.
http://dx.doi.org/10.1161/JAHA.117.006313 PMID: 30511895

[116] Verma A, Jiang CY, Betts TR, *et al.* STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015; 372(19): 1812-22.
http://dx.doi.org/10.1056/NEJMoa1408288 PMID: 25946280

[117] Rolf S, Kircher S, Arya A, *et al.* Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol 2014; 7(5): 825-33.
http://dx.doi.org/10.1161/CIRCEP.113.001251 PMID: 25151631

[118] Huang D, Li JB, Zghaib T, *et al.* The extent of left atrial low-voltage areas included in pulmonary vein isolation is associated with freedom from recurrent atrial arrhythmia. Can J Cardiol 2018; 34(1): 73-9.
http://dx.doi.org/10.1016/j.cjca.2017.10.012 PMID: 29275886

[119] Blandino A, Bianchi F, Grossi S, *et al.* Left atrial substrate modification targeting low-voltage areas for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Pacing Clin Electrophysiol 2017; 40(2): 199-212.
http://dx.doi.org/10.1111/pace.13015 PMID: 28054377

[120] Rillig A, Tilz RR, Lin T, *et al.* Unexpectedly high incidence of stroke and left atrial appendage thrombus formation after electrical isolation of the left atrial appendage for the treatment of atrial tachyarrhythmias. Circ Arrhythm Electrophysiol 2016; 9(5): e003461.
http://dx.doi.org/10.1161/CIRCEP.115.003461 PMID: 27153877

[121] Yasuda R, Murata M, Roberts R, *et al.* Left atrial strain is a powerful predictor of atrial fibrillation recurrence after catheter ablation: study of a heterogeneous population with sinus rhythm or atrial fibrillation. Eur Heart J Cardiovasc Imaging 2015; 16(9): 1008-14.
http://dx.doi.org/10.1093/ehjci/jev028 PMID: 25750193

[122] Khurram IM, Maqbool F, Berger RD, *et al.* Association between left atrial stiffness index and atrial fibrillation recurrence in patients undergoing left atrial ablation. Circ Arrhythm Electrophysiol 2016; 9(3): e003163.
http://dx.doi.org/10.1161/CIRCEP.115.003163 PMID: 26966287

[123] Patel D, Mohanty P, Di Biase L, *et al.* Outcomes and complications of catheter ablation for atrial fibrillation in females. Heart Rhythm 2010; 7(2): 167-72.
http://dx.doi.org/10.1016/j.hrthm.2009.10.025 PMID: 20022814

[124] Rostock T, Salukhe TV, Steven D, *et al.* Long-term single- and multiple-procedure outcome and predictors of success after catheter ablation for persistent atrial fibrillation. Heart Rhythm 2011; 8(9): 1391-7.
http://dx.doi.org/10.1016/j.hrthm.2011.04.012

[125] Bunch TJ, May HT, Bair TL, *et al.* Five-year outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction. J Cardiovasc Electrophysiol 2015; 26(4): 363-70.
http://dx.doi.org/10.1111/jce.12602 PMID: 25534572

[126] Pathak RK, Elliott A, Middeldorp ME, *et al.* Impact of cardiorespiratory fitness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. J Am Coll Cardiol 2015; 66(9): 985-96.
http://dx.doi.org/10.1016/j.jacc.2015.06.488 PMID: 26113406

[127] Pathak RK, Middeldorp ME, Meredith M, *et al.* Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol 2015; 65(20): 2159-69.

[128] Donnellan E, Aagaard P, Kanj M, *et al.* Association between pre-ablation glycemic control and outcomes among patients with diabetes undergoing atrial fibrillation ablation. JACC Clin Electrophysiol 2019; 5(8): 897-903.
http://dx.doi.org/10.1016/j.jacep.2019.05.018

[129] Pathak RK, Middeldorp ME, Lau DH, *et al.* Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014; 64(21): 2222-31.
http://dx.doi.org/10.1016/j.jacc.2014.09.028

[130] Fein AS, Shvilkin A, Shah D, *et al.* Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2013; 62(4): 300-305.
http://dx.doi.org/10.1016/j.jacc.2013.03.052

[131] Zhuang J, Wang Y, Tang K, *et al.* Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace 2012; 14(5): 638-45.
http://dx.doi.org/10.1093/europace/eur364

[132] Spittler R, Bahlke F, Hoffmann BA, *et al.* Predictors of successful complex catheter ablation for persistent atrial fibrillation despite failure of targeted procedural arrhythmia termination. J Cardiovasc Electrophysiol 2019; 30(7): 1026-1035.
http://dx.doi.org/10.1111/jce.13947

[133] J Albano A, Bush J, L Parker J, *et al.* Left atrial volume index predicts arrhythmia-free survival in patients with persistent atrial fibrillation undergoing cryoballoon ablation. J Atr Fibrillation 2019; 12(2): 2192.
http://dx.doi.org/10.4022/jafib.2192 PMID: 32002112

[134] Sohns JM, Vollmann D, *et al.* Left atrial volumetry from routine diagnostic work up prior to pulmonary vein ablation is a good predictor of freedom from atrial fibrillation. Eur Heart J Cardiovasc Imaging 2013; 14(7): 684-91.
http://dx.doi.org/10.1093/ehjci/jet017

[135] McGann C, Akoum N, Patel A, *et al*. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol 2014; 7(1): 23-30.
http://dx.doi.org/10.1161/CIRCEP.113.000689

[136] Khurram IM, Habibi M, Gucuk Ipek E, *et al.* Left Atrial LGE and Arrhythmia Recurrence Following Pulmonary Vein Isolation for Paroxysmal and Persistent AF. JACC Cardiovasc Imaging 2016; 9(2): 142-148.
http://dx.doi.org/10.1016/j.jcmg.2015.10.015

[137] Cheng M, Lu X, Huang J, Zhang S, Gu D. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies. J Cardiovasc Electrophysiol 2015; 26(1): 36-41.
http://dx.doi.org/10.1111/jce.12539 PMID: 25199533

[138] Schumacher K, Büttner P, Dagres N, *et al.* Association between PR interval prolongation and electro-anatomical substrate in patients with atrial fibrillation. PLoS One 2018; 13(11): e0206933.
http://dx.doi.org/10.1371/journal.pone.0206933 PMID: 30395598

[139] Park J, Kim TH, Lee JS, *et al.* Prolonged PR interval predicts clinical recurrence of atrial fibrillation after catheter ablation. J Am Heart Assoc 2014; 3(5): e001277.
http://dx.doi.org/10.1161/JAHA.114.001277 PMID: 25292186

[140] Hu X, Jiang J, Ma Y, Tang A, Novel P. Novel P wave indices to predict atrial fibrillation recurrence after radiofrequency ablation for paroxysmal atrial fibrillation. Med Sci Monit 2016; 22: 2616-23.
http://dx.doi.org/10.12659/MSM.896675 PMID: 27450644

[141] Matsuo S, Lellouche N, Wright M, *et al.* Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. J Am Coll Cardiol 2009; 54(9): 788-95.
http://dx.doi.org/10.1016/j.jacc.2009.01.081 PMID: 19695455

[142] Alcaraz R, Hornero F, Rieta JJ. Electrocardiographic Spectral Features for Long-Term Outcome Prognosis of Atrial Fibrillation Catheter Ablation. Ann Biomed Eng 2016; 44(11): 3307-18.
http://dx.doi.org/10.1007/s10439-016-1641-3 PMID: 27221509

[143] Szilágyi J, Walters TE, Marcus GM, *et al.* Surface ECG and intracardiac spectral measures predict atrial fibrillation recurrence after catheter ablation. J Cardiovasc Electrophysiol 2018; 29(10): 1371-8.
http://dx.doi.org/10.1111/jce.13699 PMID: 30016007

[144] Lankveld T, Zeemering S, Scherr D, *et al.* Atrial fibrillation complexity parameters derived from surface ECGs predict procedural outcome and long-term follow-up of stepwise catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol 2016; 9(2): e003354.
http://dx.doi.org/10.1161/CIRCEP.115.003354 PMID: 26823480

[145] Haïssaguerre M, Hocini M, Sanders P, *et al.* Localized sources maintaining atrial fibrillation organized by prior ablation. Circulation 2006; 113(5): 616-25.
http://dx.doi.org/10.1161/CIRCULATIONAHA.105.546648 PMID: 16461833

[146] Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89(4): 1665-80.
http://dx.doi.org/10.1161/01.CIR.89.4.1665 PMID: 8149534

[147] Park JH, Park SW, Kim JY, *et al.* Characteristics of complex fractionated atrial electrogram in the electroanatomically remodeled left atrium of patients with atrial fibrillation. Circ J 2010; 74(8): 1557-63.
http://dx.doi.org/10.1253/circj.CJ-10-0048 PMID: 20562494

[148] Vogler J, Willems S, Sultan A, *et al.* Pulmonary Vein Isolation Versus Defragmentation: The CHASE-AF Clinical Trial. J Am Coll Cardiol 2015; 66(24): 2743-52.
http://dx.doi.org/10.1016/j.jacc.2015.09.088 PMID: 26700836

[149] Wu SH, Jiang WF, Gu J, *et al.* Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2013; 169(1): 35-43.
http://dx.doi.org/10.1016/j.ijcard.2013.08.083 PMID: 24083885

[150] Fujimoto Y, Yodogawa K, Takahashi K, *et al.* Noninvasive evaluation of reverse atrial remodeling after catheter ablation of atrial fibrillation by P wave dispersion. Heart Vessels 2017; 32(11): 1375-81.
http://dx.doi.org/10.1007/s00380-017-1008-1 PMID: 28631077

[151] Sugumar H, Prabhu S, Voskoboinik A, *et al.* Atrial remodeling following catheter ablation for atrial fibrillation-mediated cardiomyopathy: long-term follow-up of CAMERA-MRI study. JACC Clin Electrophysiol 2019; 5(6): 681-8.
http://dx.doi.org/10.1016/j.jacep.2019.03.009 PMID: 31221354

[152] Teh AW, Kistler PM, Lee G, *et al.* Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart Rhythm 2012; 9(4): 473-80.
http://dx.doi.org/10.1016/j.hrthm.2011.11.013 PMID: 22079885