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Ablation of atrial fibrillation

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Chapter 10

Atrial remodeling and function: implications for atrial fibrillation surgery

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SUMMARY

The exact mechanism of atrial fibrillation (AF) is still incompletely understood. A number of alterations that impact focal electrical discharge, the atrial substrate and modulating factors contribute to its pathogenesis. Atrial remodeling (resulting in atrial cardiomyopathy) sets the stage for AF development. Once present, AF results in the loss of synchronized atrial contraction, which affects ventricular filling and atrial reservoir and conduit functions. Passive atrial function is particularly important in patients with left ventricular diastolic dysfunction. AF can cause tachycardiomyopathy, a mostly reversible cardiac alteration induced by tachycardia. At a structural level, atrial support is also instrumental to the function of the atrio-ventricular valves. All of these functions can be recovered to variable degrees via rhythm control strategies. Surgical and hybrid ablation show very promising results, especially in patients with a more advanced disease substrate. This review highlights the pathophysiologic aspects of AF related to left atrial function and their practical implications for surgical rhythm management.

INTRODUCTION

The exact mechanism of atrial fibrillation (AF) is multifactorial and still not completely understood¹. Atrial remodeling, resulting in atrial cardiomyopathy, sets the stage for AF development². Once present, AF causes loss of atrial mechanical function^{3,4}. In addition to palpitations, AF can cause tachycardiomyopathy - reversible alterations of ventricular function⁵. At a structural level, atrial support is instrumental to atrio-ventricular valve function⁶. These functions can be recovered through rhythm control strategies. Despite numerous studies on electrophysiology procedures and novel imaging techniques, left atrial function has not been thoroughly investigated. Also, the long-term results of percutaneous AF ablation are still far from satisfactory⁷. Standalone surgical and hybrid ablation has shown very promising results, especially in patients who are refractory to medical and transcatheter therapies⁸⁻¹⁰. Patients with heart failure (HF) could benefit from a preserved atrial function. Concomitant ablation offers the possibility to aid reverse remodeling and improve atrial function. This review highlights the pathophysiologic aspects of AF with regard to left atrial function, and aims to illustrate the practical implications for surgical rhythm management.

Pathogenesis

The pathogenesis of AF is driven by 3 elements: An electrical trigger for arrhythmia initiation, an arrhythmogenic substrate for its maintenance and modulating factors.

Electrical Trigger

A focal source in the pulmonary veins (PV) can trigger AF, and ablation of this source can prevent recurrence of AF¹¹. The mechanism inducing focal activity may involve triggered activity, rotors and localized reentry^{12,13}. Stable micro-reentrant sources have been documented as mechanisms of paroxysmal AF and in some patients with persistent AF¹⁴. Back in the 1950's, Moe and Abildskov proposed that AF can be perpetuated by continuous conduction of multiple independent wavelets activating the atrial wall in an apparently chaotic manner¹⁵. Three decades later this was confirmed both experimentally and clinically by Cox et al.¹⁶ Remote fibrillatory propagation from focal sources of AF is usually undistinguishable from multiple wavelet propagation, as it follows similar propagation patterns¹⁷.

Atrial remodeling and substrate

Stretch – caused by pressure and volume overload, but also ageing, hypertension, HF and AF itself – results in progressive structural remodeling of the atria^{18,19}. Fibroblast activation with connective tissue deposition leads to atrial fibrosis. Research has shown that already 6 weeks after the onset of AF, a significant increase in fibrosis and impaired mechanical left

atrial (LA) function is observed²⁰. In addition to fibrosis, inflammatory infiltrates, necrosis, fatty infiltration, amyloidosis and cardiomyocyte hypertrophy are commonly observed in remodeled atria^{21, 22}. These changes can lead to contractile dysfunction and chamber dilatation, and are usually more pronounced in the left atrium. Within the left atrium, the antral area tends to be affected more than the left atrial appendage (LAA)²³. Since a combination of such factors is found in many conditions predisposing for AF prior to the onset of arrhythmia, there is growing consensus that a definition of “atrial cardiomyopathy” would be more appropriate². Structural remodeling also results in alteration to ion channels, electrical dissociation between muscle bundles, and local conduction heterogeneity²⁴, favouring focal firing and electrical re-entry²⁵. Structural remodeling in the right atrium has been associated with sinus node dysfunction²⁶. Atrial dysfunction also results in a prothrombotic status due to blood stasis, which is more pronounced in the LAA. Even short AF episodes can result in a prothrombotic state due to myocardial damage and endocardial expression of prothrombotic factors²⁷. Structural remodeling is a progressive process and most of its features are only partially reversible. The treatment success of stand-alone catheter ablation appears to be related to the extent of atrial fibrosis as detected by late gadolinium enhancement magnetic resonance imaging (MRI)²⁸. Early diagnosis and aggressive treatment is important, not only for AF burden reduction but also to prevent progression of structural remodeling²⁹.

Modulating factors

Reverse remodeling does not seem to occur consistently in patients with lone AF after successful ablation³⁰. In patients with mitral stenosis and sinus rhythm, loss of cardiomyocytes and endocardial scarring is observed, suggesting atrial myopathy precedes AF³¹. In patients with MS who undergo balloon commissurotomy, reduced LA pressure promotes LA volume reduction, indicating progressive reverse remodeling³². Mitral regurgitation (MR) also leads to atrial remodeling, including fibrosis and LA dilatation³³. As is the case for mitral stenosis, reverse remodeling with LA volume reduction occurs soon after surgical correction of chronic severe MR³⁴. Aortic stenosis can also cause reversible LA dilatation, leading to a higher risk for AF³⁵.

Left atrial mechanical functions

During ventricular systole, the LA collects and stores incoming blood, serving as a “reservoir”. During the early phase of ventricular diastole, the LA empties passively into the left ventricle (LV), working as a “conduit”. Finally, through its “booster” function, during the late ventricular diastole, the LA actively “kicks” more blood into the LV.

1) The LA reservoir function is the result of an interplay between atrial compliance during ventricular systole, atrial contraction and relaxation, and apical displacement of the atrioventricular valves as a result of ventricular contraction³⁶. Because of its increased

compliance and relevant volume, the LAA contributes substantially to the reservoir function of the LA.

2) The conduit function occurs during early diastole and accounts for about one-third of the atrial flow³⁷. It is more related to LV compliance and strongly interdependent with the reservoir function. LA size increases in response to increased pressure and volume. This physiological compensation initially accounts for a gain in contraction of the atrial myocardium. Progressive dilatation and stretching of the atrial cardiomyofibers results in impaired atrial contractility, in line with the Frank-Starling curve³⁸

3) The LA booster function depends not only on the contractile properties of the atrium but also on venous return and on LV end-diastolic pressure. It accounts for about 15-30% of left ventricular filling in a normal heart under resting conditions^{3, 4, 39}.

These described LA functions can be quantified using echocardiographic speckle-tracking strain and strain rate assessment. This has made it possible to quantify these functional components of the LA independently from left ventricular diastolic function⁴⁰. Reservoir strain and strain rate are predictors of SR recovery after ablation as they are indices of atrial fibrosis and remodeling. It is currently recommended to perform echocardiography analysis to assess valvular disease, LV size and function and atrial size. Left atrial function analysis is not yet recommended, and we believe this should be included as a part of clinical and research practice, both pre-ablation and during follow-up⁹. Besides echocardiography assessment, LA functional parameters can also be measured using cardiac magnetic resonance imaging (CMRI). This has proved to provide very reliable LA function quantification⁴¹. CMRI can be used as an alternative when detailed assessment is required and is considered to be a gold standard. In addition to left atrial function analysis, CMRI offers the potential to assess atrial scars and fibrosis, which is related to the degree of atrial remodeling and ablation outcomes²⁸. However, the role of functional CMRI still needs to be evaluated in large clinical studies and is costly, time consuming and incompatible with patients who carry implanted ferro-magnetic materials. Moreover, an irregular heart rhythm reduces the image quality of CMRI compared with sinus rhythm. Improvement of the available CMRI techniques could increase the potential of this method. Furthermore, very limited data are available for CMRI in patients with AF and mitral valve disease.

Atrial mechanical function in heart failure patients

AF and heart failure can cause and exacerbate each other, while treatment of either condition may reduce the progression of both⁴². The contribution of the atrial booster pump function is believed to increase to 30-40% in the presence of impaired left ventricular filling⁴³. Reservoir and conduit functions of the left atrium are currently believed to play an important role in determining the diverse phenotypes of LV diastolic dysfunction. In fact, only a limited proportion of patients with LV diastolic dysfunction develop heart failure with preserved ejection fraction (HFpEF). Although atrial dysfunction in HFpEF has tra-

ditionally been regarded as secondary and proportional to the degree of LV impairment, recent findings suggest that mechanical LA failure is an early driver of HFpEF. Together with the loss of booster function, a global worsening of reservoir and conduit functions (reduced atrial strain) typically occurs after AF onset in these patients, and prompts a worsening of functional capacity⁴⁴.

Atrial mechanical function and ablation

The recovery of LA booster function has been traditionally regarded the main benefit of sinus rhythm recovery, although the amount of post-ablation LA contraction recovery has been found to be reduced when compared with non-ablated controls in SR⁴⁵⁻⁴⁷. It should be noted that any form of cardiac surgery alters atrial function (most probably due to adhesions following pericardiotomy), also in non-AF patients. A strict interaction was detected between postoperative LA reverse remodeling and LA contractility recovery, as a decrease of LA size favored the atrial “kick” reappearance and viceversa. Patients with lone AF have impaired myocardial energetics and subtle LV dysfunction, which does not always normalize following ablation, even after AF has been abolished⁴⁸.

Independently of rhythm outcome, the probability of recovering of active atrial contraction seems reduced once a certain degree of atrial remodeling has been reached. Tinetti et al. found recovery of LA contraction to occur only in 37% of rheumatic heart patients following concomitant maze surgery for persistent AF⁴⁹. A longer duration of AF, and the amount of atrial remodeling were found to predict AF recurrence^{49, 50}.

Scarring and electrical exclusion of areas of atrial myocardium caused by ablation surgery can impair recovery of atrial contraction⁵¹⁻⁵³. Our group demonstrated minimally invasive epicardial ablation for AF results in a significant reduction of LA conduit and reservoir function⁵².

Different lesion sets have been applied in order to preserve the LA contractile function^{45, 54}. Nevertheless, lesion sets without a posterior en-block “box” isolation of the pulmonary veins are associated with poorer efficacy¹⁰. Current echocardiography guidelines actively recommend the evaluation of LA function after AF ablation to predict the maintenance of sinus rhythm and also identify patients at risk for LA failure or arrhythmias⁵⁵.

Tachycardiomyopathy

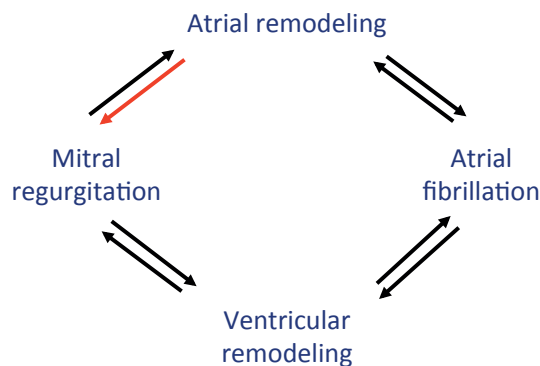
AF can lead to systolic dysfunction and ventricular dilatation. Tachycardia-mediated HF due to AF was first described in 1913,⁵⁶ but the pathogenesis is still not completely understood. Calcium overload and high-energy phosphates depletion, decreased myocardial perfusion and oxidative stress contribute to the pathogenesis of tachycardia-mediated myopathy or tachycardiomyopathy^{5, 57}. This condition affects all cardiac chambers, but the most relevant changes occur in the LV. Cardiac output is decreased, filling pressure is increased and mitral regurgitation can occur due to the loss of intrinsic contractility and progressive

dilatation without hypertrophy⁵⁸. To a lesser extent, tachycardiomyopathy affects also ventricular diastolic function due to incomplete relaxation. Most of these functional aspects of tachycardiomyopathy are reversible, although hypertrophy and diastolic dysfunction can remain⁵⁹. For these reasons, management of arrhythmia is pivotal in patients with tachycardiomyopathy. Patients with AF and HF with reduced EF (HFrEF), have proved to respond much better to rhythm control by ablation than to ablate-and-pace strategy⁶⁰. Assessing the contributory role of tachycardiomyopathy in the context of persistent AF and ventricular dysfunction remains challenging. Echocardiographic assessment may aid in determining the AF-related component⁶⁰.

Atrial function-related mitral regurgitation

LA enlargement, distension and remodeling are the main pathophysiological determinants of AF onset in patients with mitral disease. Both MR and AF-induced tachycardiomyopathy can initiate a vicious circle by promoting left ventricular dysfunction and remodelling^{60, 61} and potentially increasing mitral regurgitation (**Figure 1**). AF also promotes tricuspid and mitral annular dilatation by causing atrial remodeling and dilatation, resulting in MR and tricuspid regurgitation (TR), irrespective of left ventricular size and function^{6, 62, 63}. This “atrial functional MR” has been found to occur in up to 6% of patients undergoing AF transcatheter AF and appears to be reversible in more than two-third of patients⁶. Similarly, Maze surgery concomitant to mitral valve repair has shown to prevent dilatation of atria and the tricuspid annulus⁶⁴.

Figure 1. Interplay of atrial fibrillation, mitral regurgitation and cardiac remodeling



The role of the left atrial appendage

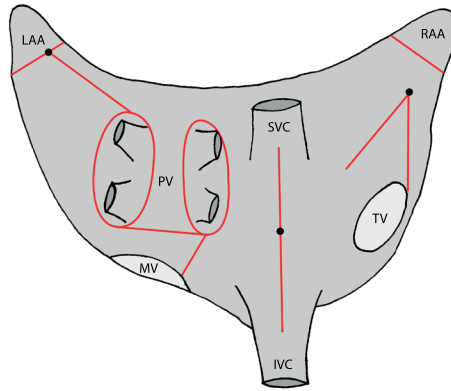
Approximately 90% of atrial thrombi in non-rheumatic AF and 60% of thrombi in patients with rheumatic mitral valve disease are found within the LAA⁶⁵. This finding prompted an increased interest in surgical and endovascular closure of the LAA. Open cardiac surgery

offers the unique opportunity to amputate, clip or suture the appendage. But complete LA exclusion has proved challenging, and incomplete closure or amputation may cause a higher risk for thromboembolic events^{66, 67}. Recently, epicardial clipping of the LAA has provided a means for a consistent occlusion and electrical isolation of the LAA^{68, 69}. However, the beneficial effect on morbidity and mortality has yet to be demonstrated. Use of the percutaneous LAA exclusion device showed no clear-cut advantage over oral anticoagulants, with a persistent risk of ischemic stroke in the device groups, and one third of the patients with a residual leak^{70, 71}. Moreover, the potential effects of LAA exclusion on LA function have not been thoroughly studied. This notwithstanding, the LAA is amputated or closed by a clip on a large scale in stand-alone and concomitant AF surgery. The recently published Clinical Practice Guidelines for the Surgical Treatment of AF have promoted a Class IIA recommendation (level of evidence C) to routinely perform LAA exclusion in patients undergoing concomitant or stand-alone ablation surgery or in any AF patient undergoing cardiac surgery⁷². The ongoing LAAOS III trial, randomizing 4700 open cardiac surgery patients to either LAA occlusion or not, will hopefully shed some light on this issue⁷³. Accurate detection of possible underlying cardiomyopathies should be pursued, and the benefits of LAA occlusion, in terms of thromboembolic prophylaxis, and possibly also in terms of rhythm control, should be balanced against the potential for hemodynamic impairment, especially in patients without persistent arrhythmias.

In recent years, novel oral anticoagulant (NOAC) medications have become available: rivaroxaban, apixaban and dabigatran. The main advantage is that NOAC do not require bloodwork monitoring and have minimal interaction with other medication. However, NOACS are not approved for patients with valvular disease. The only approved oral anticoagulant for patients with mechanical heart valves is warfarin. A randomized trial (RE-ALIGN) of dabigatran versus warfarin in patients with mechanical valves showed an increase in ischemic events and bleeding in patients using dabigatran. For AF patients without mechanical valve prosthesis, randomized controlled trials showed that NOACs were as effective (rivaroxaban and apixaban) or more effective (dabigatran) in reducing stroke risk compared with warfarin⁷⁴. Recent real-world data confirmed these results⁷⁵. Of the available NOACs, only apixaban was associated with overall mortality reduction compared with warfarin. For transcatheter ablation, NOACs have proven to be effective in periprocedural stroke risk⁷⁶. However, during stand-alone thoracoscopic pulmonary vein isolation and hybrid AF ablation warfarine is still the oral anticoagulant of choice to reduce the risk of stroke.

Concomitant AF ablation

Considering the potential benefit of reverse remodeling in patients with valvular disease, a more aggressive approach to concomitant ablation would seem reasonable. Unlike lone AF, surgical correction of the cause of volume/pressure overload, combined with Maze

Figure 2. Cox-Maze IV

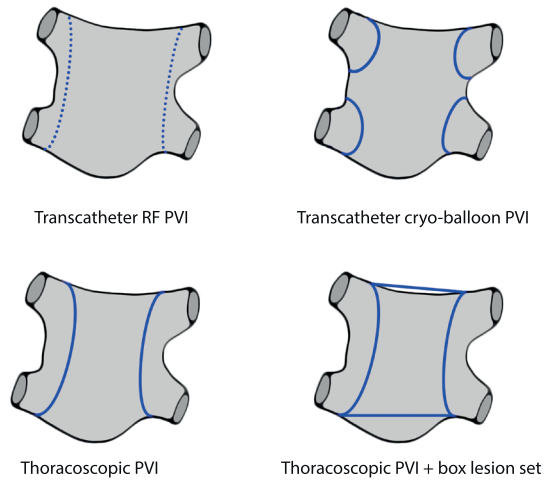
Cox-Maze IV lesion set using a bipolar radiofrequency clamp. IVC= Inferior Vena Cava, LAA= Left atrial appendage, PV= Pulmonary Veins, MV= Mitral Valve, TV = Tricuspid Valve, SVC = Superior Vena Cava

surgery (**Figure 2**), can restore atrial function. Particularly when left ventricular dysfunction is present, combining maze surgery provides the double advantage of reversing the tachycardiomyopathy and promoting reverse atrial remodeling⁷⁷. When concomitant diastolic dysfunction is present (aortic stenosis, HOCM, severe hypertension, advanced age and HFpEF in general), recovery of SR and reverse atrial remodeling provides optimal improvement of LA mechanical function, also favoring diastolic filling. Experienced centers have demonstrated that the added risk of concomitant ablation is negligible⁷⁸. Additionally, performing a concomitant maze procedure at the time of open surgery can also enhance regression of intermediate functional MR and prevent subsequent development of tricuspid regurgitation by ruling out the functional component of atrio-ventricular annulus dilation⁶⁴. LA reduction surgery proposed by some authors as an adjunct to maze, to improve rhythm outcome, must be considered with caution as it can potentially reduce the LA reservoir function⁷⁹. More extensive electrical isolation of the basal posterior LA through ablation can be a valuable and likely safer alternative for substrate modification.

Stand-alone AF ablation

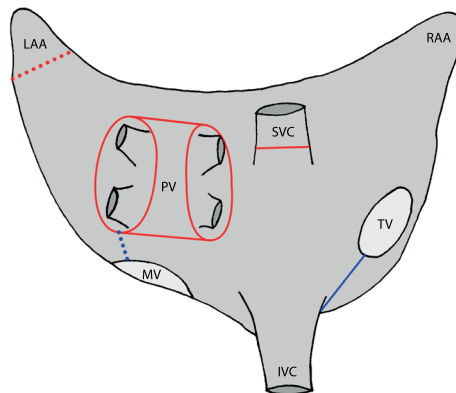
As the benefits of rhythm control for persistent and long-standing persistent AF become more evident, and the results of catheter ablation remain hampered⁷, the interest for lone AF surgery is growing^{9, 72} (**Figure 3**). Both thoracoscopic and open rhythm surgery are not likely to completely revert the underlying atrial myopathy, but they provide high probability of sinus rhythm and durable symptom relief^{8, 10}. Early stand-alone ablation can prevent tachycardiomyopathy and also improves left ventricular function⁸⁰. However, little is known on the long-term effects on cardiac function and further research is warranted on this topic. A deeper insight into atrial myopathy/remodeling would help refine the

Figure 3. Minimally invasive left atrial ablation methods



Transcatheter radiofrequency point-by-point wide circumferential ablation, Transcatheter cryo-balloon PVI, Thoracoscopic bipolar radiofrequency PVI and Thoracoscopic bipolar radiofrequency PVI with a box lesion set created with a linear bipolar ablation pen. RF= radiofrequency, PVI = Pulmonary vein isolation

Figure 4. Hybrid epi- and endocardial lesion



Hybrid epi- and endocardial lesion set, red lines depict the thoracoscopically applied lesions, blue lines depict transcatheter lesions. Dotted lines imply optional lesions; the LAA amputation (surgical) and MV isthmus line (transcatheter). IVC= Inferior Vena Cava, LAA= Left atrial appendage, PV= Pulmonary Veins, MV= Mitral Valve, TV = Tricuspid Valve, SVC = Superior Vena Cava

indications for standalone ablation surgery and would be instrumental to determining the hierarchy of the ablation procedure to be performed.

In cases of non-advanced myopathy, catheter ablation could be attempted initially, while thoracoscopic, hybrid thoracoscopic (**Figure 4**) and transcatheter ablation or even open ablation surgery may be appropriate choices for cases with advanced remodeling.

CONCLUSIONS AND IMPLICATIONS FOR AF SURGERY

Although AF is associated with impaired quality of life, stroke, HF and mortality, studies have shown that a rate control strategy is non-inferior to rhythm control, and that rhythm control is only indicated for reduction of symptoms, not for improvement of survival. Therefore, the reason for ablation must be considered carefully. The main benefits of (concomitant) ablation are symptom reduction, improvement of ventricular/cardiac function and prevention of tachycardiomyopathy. AF impairs not only the left “atrial kick”, but it also impairs the atrial reservoir/conduit function. Modern rhythm management surgery offers the unique opportunity to revert most of the negative effects of AF at a ventricular, atrial and valvular level. Because AF is a progressive disease, aggressive application of durable, transmural and continuous lesion sets can prevent electrical and structural remodeling of the left atrium. Structural assessment of atrial function and fibrosis (echocardiographically or by means of CMRI) is recommended and can aid in patient selection and may predict the capacity of re-remodeling following ablation, eventually improving ablation outcomes. To reduce the risk for thrombo-embolic events and to improve rhythm outcome, exclusion of the LAA is performed on a large scale but beneficial effect of these techniques are yet to be demonstrated. Also, the long-term effect of LAA exclusion on LA and left ventricular function is still unknown, (long-term) follow-up by means of echocardiography or cardiac MRI is recommended. A better understanding of AF pathophysiology and underlying atrial disease may help transition towards a more personalized approach to identifying more appropriate indications and guide the choice of procedure for the individual patient.

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