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# Atrial remodelling 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 remodelling (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 atrioventricular 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 pathophysiological aspects of AF related to left atrial function and their practical implications for surgical rhythm management.

**Keywords:** Atrial fibrillation • Ablation • Left atrial function • Atrial remodelling

## INTRODUCTION

The exact mechanism of atrial fibrillation (AF) is multifactorial and still not completely understood [1]. Atrial remodelling, resulting in atrial cardiomyopathy, sets the stage for AF development [2]. Once present, AF causes loss of atrial mechanical function [3, 4]. In addition to palpitations, AF can cause tachycardiomyopathy—reversible alterations of ventricular function [5]. At a structural level, atrial support is instrumental to atrioventricular valve function [6]. 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 satisfactory [7]. Stand-alone surgical and hybrid ablation has shown very promising results, especially in patients who are refractory to medical and transcatheter therapies [8–10]. Patients with heart failure (HF) could benefit from a preserved atrial function. Concomitant ablation offers the possibility to aid reverse remodelling and improve atrial function. This review highlights the pathophysiological 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 can trigger AF, and ablation of this source can prevent recurrence of AF [11]. The mechanism inducing focal activity may involve triggered activity, rotors and localized re-entry [12, 13]. Stable micro-reentrant sources have been documented as mechanisms of paroxysmal AF and in some patients with persistent AF [14]. Back in the 1950s, Moe and Abildskov [15] proposed that AF could be perpetuated by continuous conduction of multiple independent wavelets activating the atrial wall in an apparently chaotic manner. 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 patterns [17].

## Atrial remodelling and substrate

Stretch, caused by pressure and volume overload but also ageing, hypertension, HF and AF itself, results in progressive structural remodelling 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 observed [20]. In addition to fibrosis, inflammatory infiltrates, necrosis, fatty infiltration, amyloidosis and cardiomyocyte

hypertrophy are commonly observed in remodelled 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 atrial 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 a patient to AF prior to the onset of the arrhythmia, there is growing consensus that a definition of 'atrial cardiomyopathy' would be more appropriate [2]. Structural remodelling also results in the alteration of ion channels, electrical dissociation between muscle bundles and local conduction heterogeneity [24], favouring focal firing and electrical re-entry [25]. Structural remodelling in the right atrium has been associated with sinus node dysfunction [26]. 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 factors [27]. Structural remodelling 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 remodelling [29].

## Modulating factors

Reverse remodelling does not seem to occur consistently in patients with lone AF after successful ablation [30]. In patients with mitral stenosis and sinus rhythm, loss of cardiomyocytes and endocardial scarring is observed, suggesting atrial myopathy precedes AF [31]. In patients with mitral stenosis who undergo balloon commissurotomy, reduced LA pressure promotes LA volume reduction, indicating progressive reverse remodelling [32]. Mitral regurgitation (MR) also leads to atrial remodelling, including fibrosis and LA dilatation [33]. As is the case for mitral stenosis, reverse remodelling with LA volume reduction occurs soon after surgical correction of chronic severe MR [34]. Aortic stenosis can also cause reversible LA dilatation, leading to a higher risk for AF [35].

## 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 the LA actively 'kicks' more blood into the LV during the late ventricular diastole.

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 contraction [36]. 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 flow [37]. It is more closely related to LV compliance and strongly interdependent

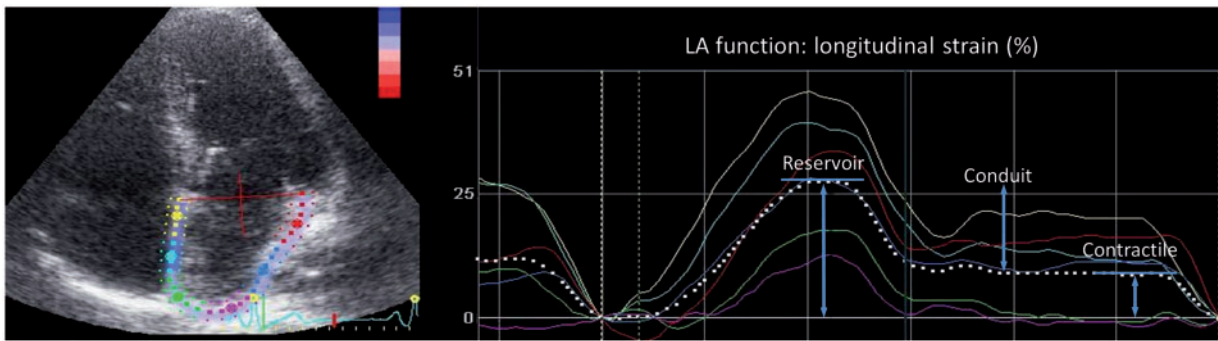
with the reservoir function. LA size increases in response to increased pressure and volume. This physiological compensation initially accounts for an increase in contraction of the atrial myocardium. Progressive dilatation and stretching of the atrial cardiomyofibres result in impaired atrial contractility, in line with the Frank-Starling curve [38].

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 (Fig. 1). This has made it possible to quantify these functional components of the LA independently from left ventricular diastolic function [40]. Reservoir strain and strain rate are predictors of sinus rhythm (SR) recovery after ablation, as they are indices of atrial fibrosis and remodelling. 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 before ablation and during follow-up [9]. 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 quantification [41]. CMRI can be used as an alternative when detailed assessment is required and is considered to be the gold standard. In addition to LA function analysis, CMRI offers the potential to assess atrial scars and fibrosis, which is related to the degree of atrial remodelling and ablation outcomes [28]. 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 ferromagnetic 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 PATIENTS WITH HEART FAILURE

AF and HF can cause and exacerbate each other, whereas treatment of either condition may reduce the progression of both [42]. The contribution of the atrial booster pump function is believed to increase to 30–40% in the presence of impaired left ventricular filling [43]. 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 HF with preserved ejection fraction (HFpEF). Although atrial dysfunction in HFpEF has traditionally 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 capacity [44].



**Figure 1:** LA function measured by longitudinal strain. Reservoir function is calculated as maximal LA wall deformation during LV systole when compared with the pre-set reference point (end diastole), conduit function as maximal LA wall deformation during early LV diastole and contractile function as the maximal LA wall deformation during late LV diastole. LA: left atrium; LV: left ventricle.

## 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 postablation LA contraction recovery has been found to be reduced when compared with non-ablated controls in SR [45–47]. 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 remodelling and LA contractility recovery, as a decrease of LA size favoured the atrial ‘kick’ reappearance, and *vice versa*. Patients with lone AF have impaired myocardial energetics and subtle LV dysfunction, which do not always normalize following ablation, even after AF has been abolished [48].

Independently of rhythm outcome, the probability of recovering of active atrial contraction seems reduced once a certain degree of atrial remodelling has been reached. Tinetti *et al.* [49] found recovery of LA contraction to occur only in 37% of patients with rheumatic heart disease following concomitant maze surgery for persistent AF. A longer duration of AF and the amount of atrial remodelling 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 contraction [51–53]. Our group demonstrated minimally invasive epicardial ablation for AF results in a significant reduction of LA conduit and reservoir function [52].

Different lesion sets have been applied to preserve the LA contractile function [45, 54]. Nevertheless, lesion sets without a posterior *en bloc* ‘box’ isolation of the pulmonary veins are associated with poorer efficacy [10]. Current echocardiography guidelines actively recommend the evaluation of LA function after AF ablation to predict the maintenance of sinus rhythm and also to identify patients at risk for LA failure or arrhythmias [55].

## 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

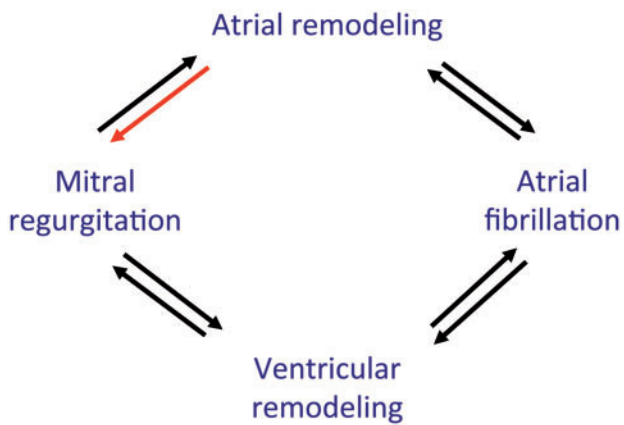
chambers, but the most relevant changes occur in the LV. Cardiac output is decreased, filling pressure is increased and mitral regurgitation can occur due to the loss of intrinsic contractility and progressive dilatation without hypertrophy [58]. To a lesser extent, tachycardiomyopathy also affects ventricular diastolic function due to incomplete relaxation. Most of these functional aspects of tachycardiomyopathy are reversible, although hypertrophy and diastolic dysfunction can remain [59]. For these reasons, management of arrhythmia is pivotal in patients with tachycardiomyopathy. Patients with AF and HFrEF respond much better to rhythm control by ablation than to ablate-and-pace strategy [60]. 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 component [60].

## ATRIAL FUNCTION-RELATED MITRAL REGURGITATION

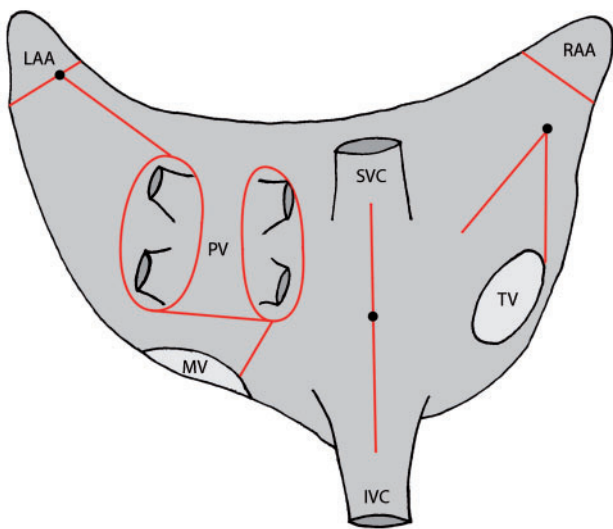
LA enlargement, distension and remodelling are the main pathophysiological determinants of AF onset in patients with mitral disease. Both MR and AF-induced tachycardiomyopathy can initiate a vicious circle by promoting left ventricular dysfunction and remodelling [60, 61] and potentially increasing mitral regurgitation (Fig. 2). AF also promotes tricuspid and mitral annular dilatation by causing atrial remodelling and dilatation, resulting in MR and tricuspid regurgitation, 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 transcatheter AF ablation and appears to be reversible in more than two-thirds of patients [6]. Similarly, maze surgery concomitant to mitral valve repair has been shown to prevent dilatation of atria and the tricuspid annulus [64].

## 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 LAA [65]. 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].



**Figure 2:** Interplay of atrial fibrillation, mitral regurgitation and cardiac remodelling.



**Figure 3:** Cox-maze IV lesion set using a bipolar radiofrequency clamp. IVC: inferior vena cava; LAA: left atrial appendage; MV: mitral valve; PV: pulmonary veins; RAA: right atrial appendage; SVC: superior vena cava; TV: tricuspid valve.

Recently, epicardial clipping of the LAA has provided a means for the 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 ischaemic 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 observation 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 surgery [72]. The ongoing Left Atrial Appendage Occlusion Study (LAAOS) III, randomizing 4700 open cardiac surgery patients to either LAA occlusion or not, will hopefully shed some light on this issue [73]. 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 haemodynamic impairment, especially in patients without persistent arrhythmias.

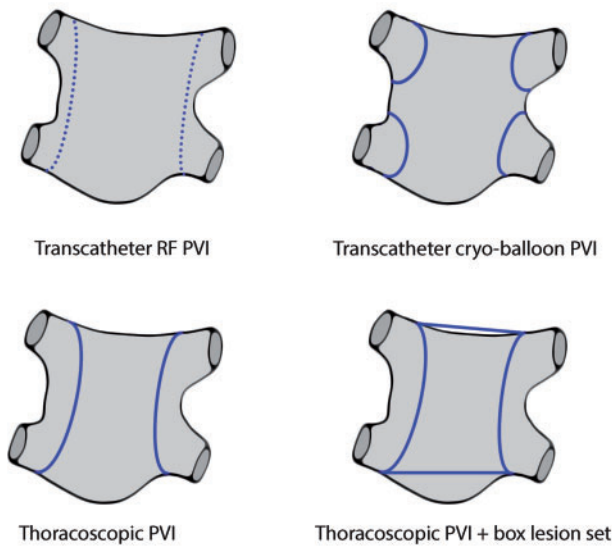
In recent years, novel oral anticoagulant (NOAC) medications have become available: rivaroxaban, apixaban and dabigatran. The main advantage is that NOAC do not require blood work monitoring and have minimal interaction with other medication. However, NOACS are not approved for patients with valvular disease. The only approved oral anticoagulant for patients with mechanical heart valves is warfarin. A randomized trial (REALIGN) of dabigatran versus warfarin in patients with mechanical valves showed an increase in ischaemic 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 warfarin [74]. Recent real-world data confirmed these results [75]. Of the available NOACs, only apixaban was associated with overall mortality reduction compared with warfarin. For transcatheter ablation, NOACs have proved to be effective in periprocedural stroke risk [76]. However, during stand-alone thoracoscopic pulmonary vein isolation and hybrid AF ablation, warfarin is still the oral anticoagulant of choice to reduce the risk of stroke.

## CONCOMITANT ATRIAL FIBRILLATION ABLATION

Considering the potential benefits of reverse remodelling 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 surgery (Fig. 3), 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 remodelling [77]. When concomitant diastolic dysfunction is present (aortic stenosis, hypertrophic obstructive cardiomyopathy, severe hypertension, advanced age and HFpEF in general), recovery of SR and reverse atrial remodelling provides optimal improvement of LA mechanical function, also favouring diastolic filling. Experienced centres have demonstrated that the added risk of concomitant ablation is negligible [78]. Additionally, performing a maze procedure concomitantly at the time of open surgery can also enhance the regression of intermediate functional MR and prevent subsequent development of tricuspid regurgitation by ruling out the functional component of atrioventricular annulus dilation [64]. 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 function [79]. More extensive electrical isolation of the basal posterior LA through ablation can be a valuable and likely safer alternative for substrate modification.

## STAND-ALONE ATRIAL FIBRILLATION ABLATION

As the benefits of rhythm control for persistent and for long-standing persistent AF become more evident, and the results of catheter ablation remain hampered [7], the interest for lone AF surgery is growing [9, 72] (Fig. 4). Both thoracoscopic and open rhythm surgery are not likely to completely revert the underlying



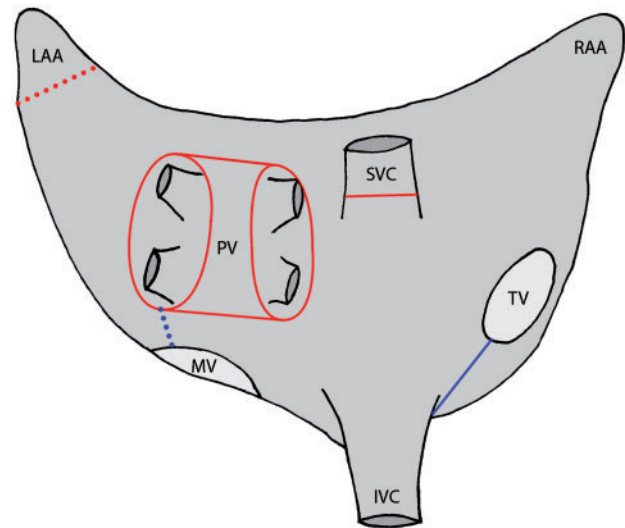
**Figure 4:** Minimally invasive left atrial ablation methods. Transcatheter radiofrequency point-by-point wide circumferential ablation, transcatheter cryoballoon PVI, thoracoscopic bipolar radiofrequency PVI and thoracoscopic bipolar radiofrequency PVI with a box lesion set created with a linear bipolar ablation pen. PVI: pulmonary vein isolation; RF: radiofrequency.

atrial myopathy, but they provide a high probability of achieving sinus rhythm and durable symptom relief [8, 10]. Early stand-alone ablation can prevent tachycardiomyopathy and also improves left ventricular function [80]. However, little is known on the long-term effects on cardiac function, and further research into this topic is warranted. A deeper insight into atrial myopathy/remodelling would help refine the indications for stand-alone 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 (Fig. 5) and transcatheter ablation or even open ablation surgery may be appropriate choices for cases with advanced remodelling.

## CONCLUSIONS AND IMPLICATIONS FOR ATRIAL FIBRILLATION SURGERY

Although AF is associated with impaired quality of life, stroke, HF and death, studies have shown that rate control is not-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 also the reservoir and conduit function. Modern rhythm management surgery offers the unique opportunity to reverse 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 remodelling 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 for re-remodelling following ablation, eventually improving ablation outcomes. To reduce the risk for



**Figure 5:** Hybrid epicardial and endocardial lesions. Hybrid epicardial and endocardial lesion set, red lines depict the thoracoscopically applied lesions, and 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; MV: mitral valve; PV: pulmonary vein; RAA: right atrial appendage; SVC: superior vena cava; TV: tricuspid valve.

thromboembolic events and to improve rhythm outcome, exclusion of the LAA is performed on a large scale, but beneficial effects 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, and (long-term) follow-up by means of echocardiography or CMRI is recommended. A better understanding of AF pathophysiology and underlying atrial disease may help the transition towards a more personalized approach to identifying more appropriate indications and make the right choice of procedure for the individual patient.

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