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Atrial Remodelling : Role in Atrial Fibrillation Ablation

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Abstract

There have been considerable advances in understanding the relationship of atrial fibrillation (AF) and atrial remodelling suggesting that remodelling states have a significant impact on treatment results.

Therefore, we reviewed the literature about the role of atrial remodelling in AF treatment, focussing on AF ablation.

Atrial fibrillatory activity, dominant frequencies (DF), complex fractionated atrial electrograms (CFAE) as well as function, volume, and fibrosis of the – especially left – atrium are most important characteristics for electrical, contractile, and structural remodelling predicting success of AF treatment. In particular, the results of AF ablation, either using catheter-based or surgical techniques, predominantly depend on the degree of structural remodelling, namely dilatation and fibrosis of the left atrium.

The available data suggest that recognizing parameters of remodelling as predictors for AF treatment facilitates differentiation between patients who may or may not benefit from the procedure and individualization of AF treatment by adapting lesion sets, by ablating additional targets, by reducing left atrial size, or by applying extended pharmacological treatment.

Introduction

Atrial fibrillation (AF), the most frequent sustained atrial arrhythmia, whose prevalence increases with age, is known as independent risk factor for stroke, heart failure, and premature death.[1-6]

During the last decades progress has been made (1) in elucidating mechanisms underlying AF and (2) in developing new techniques for AF treatment. Especially catheter-based and surgical techniques for AF ablation evolved and are now increasingly used.[7,8] However, despite relatively high success rates, sinus rhythm can not be re-established in each patient and AF may persist or recur.[7-10]

Nowadays, we realize that AF is a progressively developing arrhythmia. AF itself - as well as many other conditions – induces numerous and multifaceted alterations in atrial myocardium which are properly referred to as atrial remodelling.[11] This process can be understood as link between initiation and perpetuation of AF.

From this perspective, we undertook a review of the literature dealing with the role of atrial re-

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modelling in AF ablation. A selective literature search was carried out in the Medline database to identify original articles and reviews published in peer-reviewed journals between January 1995 and June 2012. The terms "atrial remodelling" and "ablation" as well as the Medical Subject Headings (MeSH) "atrial fibrillation", "physiopathology", "catheter ablation", and "ablation techniques" were entered for literature search. Articles were selected on the criteria that they report on human findings of atrial remodelling in AF – preferably within clinical context – and on outcome of AF treatment in relation to parameters of atrial remodelling. The current Consensus Statement on Catheter and Surgical AF Ablation as well as American and European guidelines were also included for consideration.[1,12-15]

Pathophysiological Mechanisms of AF

Trigger and Substrate

Current concepts explaining the complex pathophysiology of AF are comprehensively reviewed elsewhere.[11,16,17] In brief, the development of AF requires a trigger as well as an anatomic or functional substrate capable of both initiation and perpetuation of this arrhythmia.[18,19] Many mechanisms leading to focal ectopic generators due to abnormal impulse formation can be considered as trigger.[16] Atrial extrasystoles originating in the orificial area of pulmonary veins are typical triggers in early AF stages, whereas such sites of high-frequency activity both spread to left atrial posterior wall or other atrial regions and increase in number, later.[18,20,21] For circulating excitations perpetuating AF, formation of reentry circuits is necessary. Conditions like shortening of refractoriness, reduction of conduction velocity, inhomogeneties of impulse propagation, atrial dilatation, and tissue anisotropy serve as substrate for reentry.

Atrial Remodelling

Numerous electrical, contractile, and structural alterations of the atria occur due to AF itself (Table 1). Among these characteristic findings of atrial remodeling, shortening of atrial refractoriness, loss of atrial contractility as well as atrial dilatation and fibrosis are cornerstones of the remodelling process and crucial prerequisites for AF perpetuation, respectively. Other cardiac and extra-cardiac factors, e.g. structural heart disease, heart failure, hypertension, status of the autonomic nervous system, aging etc. (examples see Table 1), similarly change properties of atrial myocardium and contribute to initiation and perpetuation of AF.

Structural remodelling usually occurs after months, whereas electrical and contractile Remodelling develops almost immediately after AF initiation. When AF is maintained for at least 24 h, ion channel adaptation changes the electrophysiological substrate resulting in sustained reentry and increased activity of triggers supporting AF consolidation.[11, 16]

Single or multiple areas with sustained high rates – observed as dominant frequencies (DF) and complex fractionated atrial electrograms (CFAE) – may evolve due to electrical and/or structural alterations. Laboratory results suggest, that contractile remodelling goes hand in hand with electrical remodelling and that atrial dilatation during the first days of AF is primarily due to loss of atrial contractility.[41, 42] On ultrastructural level, the most conspicuous finding of remodelling is interstitial fibrosis, which may become manifest as replacement fibrosis due to myocardial cell death or reactive fibrosis due to activation of profibrotic pathways.[17,43] Obviously, factors like structural heart disease, heart failure and aging can trigger fibrosis independently from AF.

It is of importance to note, that atrial remodelling does not affect the atrial myocardium homogenously. There is strong evidence for tissue anisotropy caused by inhomogenous electrophysiological alterations and/or unevenly distributed interstitial fibrosis capable to host small and large re-entrant wavelets.[36, 44]

Electrical remodelling after re-establishing sinus rhythm reverses rapidly and completely, even after months to years of AF.[45] Renormalization of contractile remodelling strongly depends on AF duration. Echocardiographic studies after cardioversion demonstrated that atrial contractile dysfunction recovered completely within 24 hours of sinus rhythm when AF lasted 2 weeks, whereas recovery took more than 1 month when AF lasted more than 6 weeks.[46] Renormalization of structural

remodelling takes much more time and is possibly incomplete.[47]

Although well-defined animal experiments of short-term AF were able to demonstrate a close relation between different levels of remodelling,[41] clinical studies have failed to do so.[28,48] A high interindividual variability of different remodelling parameters, the missing correlation with AF duration, and the presence of additional patient- and disease-related factors, apparently hamper the detection of any supposed relationship.

Atrial Remodelling and AF Treatment

The huge variety of demographic, cardiac, and extra-cardiac factors causing or contributing to AF lead to a significant interindividual variability in patients presenting with this arrhythmia. Regarding successful AF therapy it seems therefore reasonable to choose that treatment regimen which seems to be most suitable for the individual patient. With reports on the predictive role of atrial fibrillatory rate for sinus rhythm conversion after medical AF treatment assessment of atrial remodelling came into focus in clinical medicine.[48,49] Using various techniques for assessing electrical, contractile, and structural alterations in different types of AF the role of atrial remodelling for AF treatment became clearer (Table 2).

The Role of Electrical Remodeling

Initially, electrical remodelling was investigated using high-gain, high-resolution surface ECG for analysing atrial fibrillatory activity.[48,49,68] It was shown that atrial fibrillatory frequency predicted sinus rhythm conversion after treatment of early types of the arrhythmia, mainly paroxysmal or shortstanding persistent AF, with antiarrhythmic drugs.[48,49] For treatment of longstanding persistent AF by surgical ablation, these parameters did not play any relevant role.[28] Regarding DF and CFAE as signs of electrical remodelling, there is evidence, that catheter ablation at these sites in patients with paroxysmal and persistent AF supports AF termination and prevent AF inducibility.[21,69] Nevertheless, for ablative and surgical AF treatment, it seems obvious that the longer AF persists, the more important becomes (contractile and) structural remodelling (Table 2).

Table 1 Atrial Remodelling in Humans Due to AF and Other Factors (Examples)

Factors	Electrical Remodelling	Contractile	Structural
AF	decreased depolarizing currents (↓ICaL) [22, 23] Increase in fibrillatory rate [24] Shortened APD [22, 25, 26] Loss of rate adaptation of AERP [25]	↓atrial contractility [27, 28] ↓mean peak systolic left atrial strain rate [29]	atrial dilatation [27] fibro-fatty replacement [30] fibrosis [31-33] isolated atrial amyloidosis [34]
Factors other than AF			
structural heart disease	decreased depolarizing currents (↓ICaL) [35]		fibrosis [33, 36, 37] isolated atrial amyloidosis [34]
aging	pulmonary veins arrhythmogenesis [38]		atrial dilatation [39] replacement and reactive fibrosis [40] isolated atrial amyloidosis [34]

APD, action potential duration, AERP atrial effective refractory period

The Role of Contractile Remodelling

Contractile remodelling usually assessed by echocardiographic parameters plays a role most notably for pharmacological and electrical cardioversion and ablation of early AF types.[52,56,57]It seems to be less important for surgical ablation of longstanding AF, although we could demonstrate a weak trend in univariate analysis toward better atrial contractility in patients who regained sinus rhythm after AF ablation and mitral valve surgery.[28] At least two reports on catheter ablation of paroxysmal and persistent AF suggest that left atrial function assessed by 2D speckle tracking before ablation or by intracardiac Doppler measurement after ablation predicts AF recurrence.[57,58]

The Role of Structural Remodelling

Several studies (Table 2) have demonstrated, that structural remodelling plays the most prominent role for rhythm outcome after AF treatment. Left atrial dilatation, precisely assessed as left atrial volume by multi-slice CT imaging, is one of the strongest predictors of rhythm outcome following AF ablation.[64,70] Patients with left atrial volume greater than 135 ml are likely to develop recurrent AF after catheter ablation.[64] For practical reasons, echocardiographic measurement of the end-systolic left atrial dimension in the parasternal long axis view is widely used to determine the eligibility for AF ablation with cut-offs of 5 or 5.5 cm, although this parameter correlates poorly with true left atrial volume.[13, 70] For surgical AF treatment, either by ablation or by cut-and-sew maze procedure, left atrial size was also demonstrated to be an important predictor for AF recurrence.[10,28,66,67] The cut-off value for left atrial size was 56.8 m for treatment of persistent AF by radiofrequency maze procedure with concomitant mitral valve surgery.[66]

As suggested by one group, visualization and quantification of atrial fibrosis by cardiac delayed enhanced magnetic resonance imaging (DE-MRI) could be useful for more individualized stratification.[62] However, further efforts are required to validate the predictive accuracy of DE-MRI-detected fibrosis in predicting outcomes of AF ablation, before this elaborate technique should be introduced into clinical routine.

According to experimental data, beneficial effects of pharmacological therapy by ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists on structural remodelling could be expected, especially by antifibrotic effects.[14,71] Although supported by previous clinical trial data,[72-74] this concept of renin-angiotensin system inhibition for so-called upstream therapy has failed to demonstrate convincing clinical results regarding the burden of AF and changes in left atrial dimensions in recent randomized controlled trials.[75, 76] Now, there is very little reason to consider such therapy in patients with less or no structural heart disease .[15] However, the impact of upstream therapy on atrial fibrosis in AF patients undergoing ablative treatment needs further clarification.

Conclusions for AF Ablation

Today, AF treatment by catheter ablation is clearly indicated (class I, level A) in symptomatic patients with paroxysmal AF refractory or intolerant to antiarrhythmic drug therapy.[13,15] Furthermore,

Table 2 Reports On Role of Atrial Remodelling in AF Treatment

AF Treatment	Remodeling	Type of AF		
		Paroxysmal	Persistent	longstanding Persistent
Pharmacologic cardioversion	electrical	• [48-51]	• [48-51]	-
	contractile	-	• [52]	-
	structural	• [49, 53]	• [49, 53]	-
Electrical cardioversion	electrical	-	• [54, 55]	-
	contractile	-	• [52, 56]	-
	structural	• [53]	• [53, 55]	-
Catheter ablation	electrical	-	-	-
	contractile	• [57]	• [57, 58]	• [58]
	structural	• [59-63, 64]	• [59, 60, 62, 64]	• [60]
Surgical ablation	electrical	-	-	-
	contractile	-	-	• [28]*
	structural	• [10, 65]	• [10, 65, 66]	• [10, 28]
(cut-and-sew-) Maze operation	electrical	-	-	-
	contractile	-	-	-
	structural	• [67]	• [67]	• [67]

* univariate Analysis

catheter ablation is reasonable (class IIa, level B) in (1) symptomatic patients with persistent AF refractory or intolerant to antiarrhythmic drug therapy and (2) in selected patients with symptomatic paroxysmal AF as first-line treatment, when patient choice, benefit, and risk are considered.[13,15] AF treatment by concomitant surgical ablation is reasonable (class IIa, level C) in (1) symptomatic patients with all types of AF refractory or intolerant to antiarrhythmic drug therapy and in (2) symptomatic patients with paroxysmal or persistent AF prior to initiation of antiarrhythmic drug therapy.[13]

Despite these clear indications for AF ablation, evaluation of potential benefits and risks of procedural failure or complications is necessary for individual decision making. Predictors of rhythm outcome may help to stratify treatment options. Remodelling parameters which have been demonstrated to predict rhythm outcome after surgical or catheter ablation and techniques for their assessment are summarized in Table 3. There is consensus, that patients with advanced remodelling need to be adequately counselled on their higher risk of treatment failure. In this group it is necessary to perform more extensive ablation and/or to do a more aggressive LA reduction in patients undergoing cardiac surgery.[10, 60, 62] However, as long as the value of these additional procedures is indefinite we should be cautious adding something if there is any chance that it might increase periprocedural risk. Furthermore, the data published so far are not sufficient to determine general thresholds of remodelling parameters. Thus, appropriate cut-off values – with special regards to structural remodelling - should be defined and proved based on particular local conditions (patient cohorts, ablation procedures, experience, results, follow up, etc.).

Summary

There have been considerable advances in under-

Table 3 Remodelling Parameters as Predictors for Rhythm Outcome After Ablation of Different AF Types and Techniques for Their Assessment

Technique	Parameter	Reference	Type of AF		
			Paroxysmal	Persistent	Long-Standing Persistent
Echocardiography	LA Diameter	[59]			
(TTE, TEE)		[10]			
		[66]			
	LA Volume	[63]			
	LA Strain	[57]			
Computed Tomography	LA Volume	[60]			
(MDCT)		[64]			
		[61]			
	RA Volume	[61]			
Magnet Resonance Imaging	LA Volume	[62]			
(DE-MRI)	LA Fibrosis	[62]			

TTE, transthoracic echocardiography, TEE, transesophageal echocardiography, MDCT, multi-detector computed tomography, DE-MRI, delayed enhanced magnetic resonance imaging, LA, left atrial, RA, right atrial, light grey, catheter ablation, dark grey, surgical ablation

standing the relationship of AF and atrial remodelling and its impact on the progressive course of this arrhythmia. Moreover, recognizing parameters of remodelling as predictors for AF treatment – in particular the role of structural remodelling for AF ablation – helps us (1) to differentiate between patients who may or not benefit from the procedure and (2) to individualize AF treatment by adapting lesion sets, ablate additional targets, reduce left atrial size, or apply extended pharmacological treatment targeting reverse remodelling. However, for individual decision making there is urgent need for further clinical studies defining appropriate cut-off values of structural remodelling and testing the efficacy of accordingly adapted treatment strategies.

Disclosures

No disclosures relevant to this article were made by the authors.

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