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REVIEW

New Insights into Mechanisms of Atrial Fibrillation

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Summary

Although atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, precise mechanisms that lead to the onset and persistence of AF have not completely been elucidated. Over the last decade, outstanding progress has been made in understanding the complex pathophysiology of AF. The key role of ectopic foci in pulmonary veins as a trigger of AF has been recognized. Furthermore, structural remodeling was identified as the main mechanism for AF persistence, confirming predominant role of atrial fibrosis. Systemic inflammatory state, oxidative stress injury, autonomic balance and neurohormonal activation were discerned as important modifiers that affect AF susceptibility. This new understanding of AF pathophysiology has led to the emergence of novel therapies. Ablative interventions, renin-angiotensin system blockade, modulation of oxidative stress and targeting tissue fibrosis represent new approaches in tackling AF. This review aims to provide a brief summary of novel insights into AF mechanisms and consequent therapeutic strategies.

Key words

Atrial fibrillation • Triggers • Electrical remodeling • Structural remodeling • Fibrosis

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia that affects approximately 1 % of the general population and up to 8 % of subjects over the age of 80 years (Fuster *et al.* 2006). AF is associated with decreased quality of life, increased morbidity and a 30 % higher risk of death (Benjamin *et al.* 1998), and thus is a major contributor to cardiovascular mortality. Up to 15 % of all strokes are attributable to this disorder. AF is characterized by very rapid, chaotic electrical activity of the atria, resulting in accelerated and irregular ventricular activity, loss of atrial mechanical function and increased risk of atrial clot formation. AF can occasionally affect a structurally normal heart of otherwise healthy individuals (so-called "lone AF"), but most typically it occurs in subjects with previous cardiovascular damage due to hypertension, coronary artery disease and diabetes. The aim of this article is to review current understanding of the mechanisms responsible for the onset and persistence of the arrhythmia with emphasis on the role of atrial fibrosis as the main course of structural remodeling.

Conceptual models of atrial fibrillation

The mechanisms of spatiotemporal organization of electrical activity in the atria during AF have not conclusively been understood. Three models were proposed (Garrey 1924) but applicability of these models is still disputed. The *focal mechanism theory* with fibrillatory conduction stands on the notion that AF is provoked and perhaps also driven further by the rapid firing of a single or multiple ectopic foci. This theory has gained recent support from clinical observation by Haissaguere *et al.* (1998) that paroxysmal AF can be cured by focal ablation of ectopic activity in the pulmonary veins. The *single circuit re-entry theory* of AF

assumes the presence of a single dominant re-entry circuit – "mother rotor" with a break-up of emanating waves in the atrial tissue of variable electrical properties. The *multiple wavelet theory* of AF assumes the presence of multiple reentry circuits with randomly propagating wave-fronts that must find receptive tissue in order to persist (Moe *et al.* 1964). The shortening of the refractory period of atrial myocytes and the slowing of conduction velocity – salient features of electrical remodeling – both help to stabilize the arrhythmia by decreasing circuit size. This theory has support in the experimental work of Allessie *et al.* (1985). It appears that all three concepts are non-exclusive and each may be applicable to certain subgroups of AF patients, or that they may even coexist in the same subject during different stages of AF development.

The probability of development of AF is also affected by external modifiers. According to Coumel´s triangle of arrhythmogenesis, three cornerstones are required in the onset of clinical arrhythmia (Farré and Wellens 2004) – the arrhythmogenic substrate, the trigger factor and the modulation factors such as autonomic nervous system or inflammation. The interplay between trigger, substrate and the modulation factors determines the clinical picture of the arrhythmia. In the absence of a significant substrate for AF persistence, i.e. in a structurally normal heart, the triggering ectopic activity leads to self-terminating episodes of AF – paroxysmal AF. On the other hand, even limited ectopy in extensively remodeled atria can start AF that persists until its termination by cardioversion (persistent AF) or indefinitely (permanent AF). Once established, AF itself alters electrical and subsequently structural properties of the atrial tissue and these changes cause or "beget" further AF self-perpetuation (Wijffels *et al.* 1995).

Triggers of atrial fibrillation

Role of the pulmonary veins

Twelve years ago, Haissaguerre *et al.* (1998) published a landmark observation describing the causal role of pulmonary veins in the inception of AF. However, the mechanism of impulse initiation in the pulmonary veins has still not been defined. Abnormal automaticity, triggered activity and the re-entry mechanism were proposed.

There is more evidence showing that the pulmonary veins are capable of automaticity. Specialized cardiac cells associated with pacemaking, resembling pale (P) and Purkinje cells, have been observed in the pulmonary veins in rats, dogs and humans (Wit and Boyden 2007). These cells might be residua of the embryonic myocardium. Developmental studies have shown that the complicated looping process of the heart tube brings together the essential parts of the sino-atrial and primary ring myocardium which are embryonic precursors of definitive conduction system. During this development, sino-atrial tracts are formed that run between the sino-atrial and the atrio-ventricular node, together with tracts surrounding the pulmonary veins and the coronary sinus (Gittenberger-de Groot *et al.* 2003).

Honjo *et al.* (2003) showed that infusion of ryanodine, an inhibitor of Ca^{2+} release from the sarcoplasmic reticulum, shifts the cardiac pacemaker from the sino-atrial node to a focus near the right pulmonary vein. Zhou *et al.* (2002) demonstrated that such focal activity within the pulmonary veins may be enhanced in persistent AF, suggesting that pulmonary veins may not only provoke AF, but they may also be important in sustaining re-entry. This may consequently contribute to AF persistence. Experiences with AF ablation show that radiofrequency elimination of such foci within PV may terminate the arrhythmia.

The myocardial architecture in human pulmonary veins is highly variable. The transition from atrial to venous walls is gradual as the left atrial myocardial sleeves overlap with smooth muscle of the venous myocardium (Ho *et al.* 1999). The muscle fibers in pulmonary veins are usually orientated perpendicularly to the blood flow. Such an arrangement, together with increased anisotropy due to ageing-induced fibrosis, may facilitate re-entry within the pulmonary veins. Furthermore, the cellular properties of pulmonary-vein cardiomyocytes, such as shorter action potential and smaller zero-phase upstroke velocities than in the left atrium, are in favor of re-entry (Ehrlich *et al.* 2003).

Triggers of atrial fibrillation as a therapeutic target

Optical mapping studies documented the location of preferential re-entry circuits that occur in the pulmonary vein region in canine models of AF (Arora *et al.* 2003). Electrophysiological studies in patients with paroxysmal atrial fibrillation found re-entry circuits located mainly at the junction of pulmonary vein and left atrial junction (Atienza *et al.* 2006). Accordingly, the pulmonary veins emerged as a potential target for ablation. Several approaches were developed: focal ablation within the pulmonary veins, followed later by

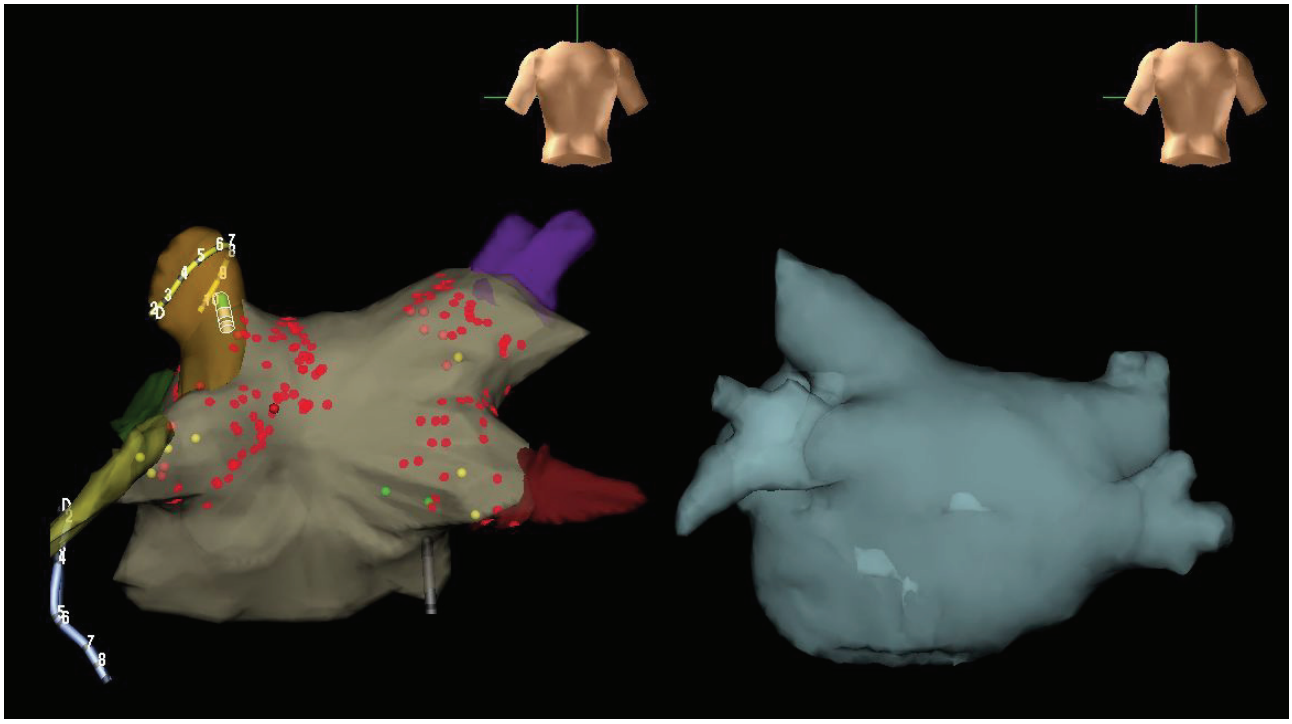

Fig. 1. Scheme of circumferential lesions created in patients with paroxysmal atrial fibrillation undergoing catheter ablation and isolation of pulmonary veins. Ablation sites (red dots) are projected on 3D map of the left atrium in posterior view obtained by means of Nav X mapping system (St. Jude Medical). On the right side of the panel is corresponding CT angiogram of the left atrium and pulmonary veins.

segmental ostial ablation guided by pulmonary vein potentials or circumferential pulmonary vein ablation, and the creation of linear lesions. Currently, circumferential ablation in combination with linear lesions in both atria appears to be the most effective approach (Fig. 1). This complex procedure carries a significantly higher success rate, with about 85 % of patients with paroxysmal AF being cured and antiarrhythmic drug free.

Other focal triggers of atrial fibrillation

Triggered activity similar to pulmonary vein foci has been seen in the musculature of other cardiac structures. Focal atrial tachycardia and fast repetitive activity after rapid atrial-pacing have been shown to originate from the musculature of the coronary sinus, the superior vena cava, and the ligament of Marshal (Wit and Boyden 2007).

Optical mapping-studies in animal models point to a dominant role of the posterior left atrium in sustaining AF (Atienza and Jalife 2007) where the AF is maintained by functional micro-reentry circuits localized in the proximity of the junction of the pulmonary veins and the left atrium. During the isolation of pulmonary veins by radiofrequency energy, AF terminates usually before the full electrical isolation is accomplished, probably due to disruption of these re-entry circuits at the posterior left atrium. From our clinical experience, greater procedural success is achieved if radiofrequency isolation of the pulmonary vein is accomplished with larger encircling lesions that cover most of the posterior wall of the left atrium. Another approach has been advocated by Nademanee *et al.* (2004), consisting of mapping areas with complex and fractionated electrograms and subsequent catheter ablation. These sites may reflect regions with functional micro-reentrant circuits or firing of the autonomic ganglia. Catheter ablation of these spots is able to abolish AF without the need for isolation of the pulmonary veins.

Modifiers of AF substrate

The autonomic nervous system

An imbalance in autonomic nervous system activity can result in significant changes of cardiac electrophysiological properties of the atrial myocardium which may facilitate the induction of AF. Vagal nerve stimulation causes the shortening of an effective refractory period and facilitates induction of AF and re-entrant atrial arrhythmias (Zipes *et al.* 1974). Patients with this vagal-dependent AF are mostly middle-aged males without structural heart disease but with high basal

parasympathetic tone. Increased sympathetic tone may also facilitate the development of AF. Modification of sympathetic responsiveness by adrenergic beta-receptor blockade might be useful in preventing AF recurrence after sinus rhythm restoration (Kühlkamp *et al.* 2000). Excessive adrenergic stimulation is believed to be dominant mechanisms in postoperative AF. Prophylactic use of beta-blockers reduces the incidence of postoperative AF (Maisel *et al.* 2001).

The cardiac autonomic nervous system can be divided into extrinsic and intrinsic components (Ardell 1994). The extrinsic part consists of brain nuclei and chains of ganglia along the spinal cord with axons terminating in the heart. The intrinsic component is composed of a network formed of axons and autonomic ganglia (ganglion plexus) embedded within epicardial fat pads located above both atria and ventricles (Armour *et al.* 1997). One important part of the ganglion plexus has been located in close proximity to the left-atrial pulmonary vein junction. This area is rich in autonomic innervations. Recent studies have shown that stimulation of the plexus in this location can convert focal activity in the pulmonary veins into AF (Scherlag *et al.* 2005).

Autonomic nervous system as a therapeutic target

Some research groups have hypothesized that elimination of the ganglion plexus, particularly at the pulmonary-vein atrial junction, could increase the success rate of AF ablation (Pappone *et al.* 2004). In an experimental study in dogs, radiofrequency ablation of epicardial fat pads substantially reduced the inducibility of AF during vagal stimulation which immediately followed the ablation procedure. However, after 4 weeks of recovery, the AF inducibility was unchanged in comparison to the baseline (Oh *et al.* 2006). The anatomy of the pulmonary-vein atrial junction seems to be more complex than previously thought. Adrenergic and cholinergic nerves have the highest densities within 5 mm on the atrial side of the junction, and they are highly co-located (Tan *et al.* 2006). This makes selective ablation of either vagal or sympathetic nerves in this location practically impossible. Furthermore, after catheter ablation in these sites, a sympathetic hyperinnervation could follow due to neural plasticity (Okuyama *et al.* 2004). Radiofrequency catheter ablation is followed by significant elevation of the systemic nerve growth factor concentrations (Kangavari *et al.* 2006). This may well play a role in early recurrence of AF after ablation. Further studies in this area are needed to elucidate the benefit of ganglionic plexus ablation in AF therapy.

Atrial substrate and remodeling

Remodeling involves changes in the structure, function and geometry of the atria, modifications of atrial electrical and contractile properties, and changes in the amount and the composition of the extracellular matrix. Together, these alterations create an arrhythmogenic substrate essential for the persistence of AF. An important source of atrial remodeling can be AF itself, mainly due to the effects of rapid atrial rate and elevated filling pressure. Another cause of remodeling are cardiovascular factors damaging the heart even prior to the onset of arrhythmia; namely hypertension, coronary disease, diabetes or hemodynamic overload due to valve disease. There are two distinct forms of atrial remodeling – electrical and structural, which differ in etiology, involved mechanisms and potential reversibility (Table 1). Electrical remodeling occurs due to the effects of a high atrial rate and includes changes in ionic properties of the atrial myocytes, particularly the shortening of refractoriness and the slowing of conduction velocity (Pandozi *et al.* 1998).

Electrical remodeling

The concept of atrial remodeling due to chronic high atrial rates or "tachycardia-induced electrical remodeling" was first described in experimental studies (Morillo *et al.* 1995, Wijffels *et al.* 1995). It has been found in animal models that AF is sustained due to marked shortening of the atrial refractory period and due to an abnormal rate-adaptation of refractoriness, and that these changes involve alterations of intracellular Ca^{2+} handling. With each action potential, Ca^{2+} enters the cell through L-type Ca^{2+} channels. Under the conditions of high atrial rate, Ca^{2+} loading is substantially enhanced. Cardiomyocytes prevent dangerous Ca^{2+} overload by the activation of short-term and long-term protective mechanisms, such as functional inactivation L-type calcium current (I_{CaL}) or down-regulation of mRNA encoding L-type calcium channels (Yue *et al.* 1997). A significant reduction in the Na^{+} current (I_{Na}) density was also reported in a dog model (Gaspo *et al.* 1997). The decrease in I_{CaL} leads to a reduction in the action potential duration, whereas the reduction in the I_{Na} may contribute to the decrease in the conduction velocity. These changes concurrently facilitate the re-entry mechanism. However, electrical remodeling is

Table 1. Two forms of atrial remodeling.

	Electrical	**Structural**
Cellular and tissue characteristics	Alterations in ionic changes L-type, Ca^{2+} current down-regulation	myocyte loss, diffuse and patchy fibrosis, scarring
Refractory period	↓↓↓	↔
Conduction velocity	↔ or ↑	↓↓
Clinical scenario	Atrial tachycardia, paroxysmal AF	AF in CHF
Animal model	Rapid atrial pacing (Wijffels *et al.* 1995)	Rapid ventricular pacing (Li D *et al.* 1999)
Reversibility	+ + +	–

still completely reversible after restoration of sinus rhythm. In fact, even after prolonged periods of AF (months to years), the atrial refractoriness returns to normal within a few days after sinus rhythm restoration.

The propensity to develop and sustain arrhythmia can be modified by the administration of antiarrhythmic drugs. The most frequently used drugs for rhythm control in AF patients are class I and III antiarrhythmic agents, which are typically sodium-channel or potassium-channel blockers, respectively.

The main electrophysiologic effect of many antiarrhythmic drugs is prolongation of the atrial action potential, reversing so electrical remodeling. Prolongation of action potential in the atria can then prevent recurrence of AF. Amiodarone prevented tachycardia-induced atrial electrophysiological remodeling, both at the level of atrial electrical properties and ion-channel subunit expression (Shinagawa *et al.* 2003). However, the effects of antiarrhythmic drugs in tissue affected by AF are reduced. In a mathematical model of the human atrial myocyte electrophysiology, the effect of I_{Kr} blockade on the duration of the action potential was reduced in remodeled atrial cells (Courtemanche *et al.* 1999). In AF-remodeled goat atria, the effects of dofetilide on refractoriness were decreased (Blaauw *et al.* 2004). Similarly, flecainide has reduced efficacy in atrial tissue changed by tachycardia-induced remodeling, but it recovers its antiarrhythmic action after cardioversion of AF (Teileman *et al.* 2005).

Structural remodeling

The second and probably more important form of atrial remodeling is "structural remodeling". Experimental studies (Ausma *et al.* 1997) demonstrated that prolonged rapid atrial pacing induces changes in atrial myocytes such as an increase in cell-size, myolysis, perinuclear accumulation of glycogen, alterations in connexin expression, fragmentation of sarcoplasmic reticulum and changes in mitochondrial shape. At the tissue level, structural remodeling is characterized by myocyte cell loss, and by changes in extracellular matrix composition, with both diffuse interstitial and patchy fibrosis. Similar alterations were also observed in the atrial tissue of patients with AF (Frustaci *et al.* 1997). Structural remodeling results in electrical tissue non-homogeneity, slowed conduction and electrical uncoupling, facilitating AF continuation without inducing changes in atrial action potential properties. In contrast to electrical remodeling, structural changes are far less reversible and they tend to persist even after the re-establishment of sinus rhythm.

Structural remodeling can also precede the onset of AF since it emanates from cardiac damage due to coronary artery disease, hemodynamic overload from valve disease or hypertension. Interestingly, incident AF in the Framingham study was not related to mean arterial blood pressure, but it was much more predicted by pulse pressure, a surrogate marker of arterial stiffness (Mitchell *et al.* 2007). This suggests that cardiac atrial fibrosis in hypertensive patients may be a part of more widespread changes in the extracellular matrix of the cardiovascular system, affecting not only the heart but also the large arteries.

An illustrative example of structural remodeling are changes observed in the atria in chronic heart failure (CHF), characterized by dilatation of the atria, with marked diffuse and patchy interstitial fibrosis and scarring. The degree of structural pathology relates to the degree of LA enlargement. In human atrial specimens, the amount of fibrosis was greater in the atria of patients with AF as opposed to those with sinus rhythm (Boldt *et al.* 2004). Structural remodeling explains why CHF is the most common clinical cause of AF and why CHF precedes AF about as often as AF precedes CHF.

Mechanisms of atrial fibrosis

The precise mechanism and signaling pathways involved in structural remodeling and atrial fibrosis are still unknown. The renin-angiotensin system, the transforming growth-factor β1 (TGF-$ß_1$) pathway, inflammation and reactive oxygen species are involved in the development of atrial fibrosis. Profibrotic signals act on the balance between matrix metalloproteinases (MMPs) – main enzymes responsible for degradation of extracellular matrix – and their local tissue inhibitors (TIMPs). Furthermore, profibrotic signals stimulate the proliferation of fibroblasts and extracellular deposition of fibronectin, collagens I and III, proteglycans and other matrix components.

The renin-angiotensin system

The development of atrial fibrosis in CHF is angiotensin-II dependent. Li *et al.* (2001) showed in a canine CHF model, that atrial angiotensin-II concentrations and mitogen-activated protein kinases (MAPKs) were increased by ventricular pacing, together with substantial changes in phosphorylated forms of c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38-kinase. In addition, enalapril significantly reduced tachypacing-induced changes in atrial angiotensin-II concentrations and ERK expression. Increased tissue angiotensin-II and phosphorylated MAPKs are associated with apoptosis, leukocyte infiltration, and tissue fibrosis (Cardin *et al.* 2003). The effects of angiotensin-II on extracellular matrix composition and collagen expression are partly mediated by the local production of cytokine TGF-$ß_1$ (Kupfahl *et al.* 2000).

TGF-$ß_1$/SMAD pathway

TGF-$ß_1$ is a profibrotic cytokine that controls the production and composition of the extracellular matrix in many tissues including the heart, vessel wall, the lungs and the liver (Khan and Sheppard 2006). Overexpression of TGF-$ß_1$ enhances extracellular matrix synthesis and organ fibrosis. In the cardiovascular system, TGF-$ß_1$ plays an important role in scar formation after myocardial infarction, cardiac hypertrophy, the stabilization of atherosclerotic plaque (Cipollone *et al.* 2004) and in atrial scarring due to CHF (Everett and Olgin 2007).

TGF-$ß_1$ production in the myocardium is increased by angiotensin-II (Campbell and Katwa 1997) and AT_1 receptor-antagonists inhibit TGF-$ß_1$ gene expression (Kim *et al.* 1995). Importantly, administering of angiotensin-II does not induce cardiac hypertrophy in mice lacking the TGF-$ß_1$ gene (Schultz *et al.* 2002). Following the synthesis in cardiac fibroblasts and release into the extracellular space, TGF-$ß_1$ binds to the TGF-$ß_1$ receptor. This leads to the phosphorylation of intracellular SMAD proteins that form complexes which translocate into the nucleus where they regulate DNA transcription. In addition, the activation of the TGF-$ß_1$ receptor also leads to the expression of a connective-tissue growth-factor (CTGF) that is released locally and acts in a paracrine way which further stimulates extra-cellular matrix-protein expression and fibrosis.

The critical role of the TGF-$ß_1$ pathway in the incidence of AF has been shown in transgenic mice overexpressing constitutively active form of TGF-$ß_1$ which led to selective atrial fibrosis, increased conduction heterogeneity and enhanced AF susceptibility, despite normal atrial action potential duration and normal ventricular structure and function (Verheule *et al.* 2004).

Cardiac fibrosis driven by TGF-$ß_1$ is negatively regulated by the bone morphogenic protein 7 (BMP-7) which also belongs to the TGF superfamily and uses SMADs for intracellular signaling. Systemic administration of the human recombinant BMP-7 inhibited cardiac fibrosis in a pressure-overloaded mouse model (Towbin 2007). It remains to demonstrate whether BMP-7 also plays a role in the structural remodeling of atria and risk of AF.

Inflammation and reactive oxygen species

Histological studies noted inflammatory cell infiltration and fibrosis in atrial biopsies of patients with lone AF (Frustaci *et al.* 1997). Inflammatory cell infiltration and calcium overload during high atrial rate may promote oxidative damage in atrial tissue which promotes atrial fibrosis and facilitates AF continuation. There is increasing evidence that oxidative stress and inflammation are relevant players in structural atrial remodeling.

The causal link between inflammation and AF was first proposed by Bruins *et al.* (1997). In patients who underwent coronary artery bypass surgery, the peak incidence of postoperative AF coincided with the peak in C-reactive protein (CRP) elevation. In a population study of 5,806 subjects aged 65 years or older, baseline CRP level predicted the future development of AF (Aviles *et al.* 2003). Moreover, lower hs-CRP at the baseline was associated with maintenance of sinus rhythm after planned electrical cardioversion for persistent AF (Tveit *et al.*

2007). CRP may not be just a marker of current inflammation, but it may itself contribute to cardiac damage by activating the serum complement (Pepys *et al.* 2006). Whether complement-mediated inflammation plays a role in human AF remains to be demonstrated.

Mihm *et al.* (2001) showed that oxidative damage in the atrial myocardium of chronic AF patients is due to the local action of hydroxyl radicals and peroxynitrite. In a dog model, atrial tachy-pacing led to a decrease of ascorbic acid in the atrial tissue and to increased protein nitration (Carnes *et al.* 2001).

Examination of gene transcriptional profiles of human atrial tissue of AF patients showed a shift toward the pro-oxidative gene expression (Kim *et al.* 2003). The main contributors to atrial oxidative stress were myocardial NADPH-oxidase and uncoupled NO synthase (Kim *et al.* 2005). Furthermore, reactive oxygen species were indirectly stimulated by activation of the renin-angiotensin system. Activation of AT_1 receptors increased NADPH oxidase-mediated superoxide production, and inhibition of AT_1 receptors decreased oxidative stress in the vascular wall (Keaney 2005).

Structural remodeling as a therapeutic target

Modulation of the renin-angiotensin-aldosterone system

Because angiotensin II has a central role in the development of atrial fibrosis, inhibition of atrial ACE and AT_1 receptors might be beneficial in AF. In experimental models, AF susceptibility and atrial fibrosis were decreased by candesartan or enalapril, but not by hydralazine or isosorbide mononitrate despite similar hemodynamic effects (Okazaki *et al.* 2006, Li *et al.* 2001), thus suggesting a key role of targeting renin-angiotensin system, rather than of improving the hemodynamics. Meta-analysis of all trials using ACE inhibitors or angiotensin receptor blockers (ARB) showed that these drugs have quite potent antiarrhythmic effects. In the overall population, these drugs reduced new-onset AF by 18 %, and among heart failure patients as much as 43 % (Anand *et al.* 2006). Blockade of the renin-angiotensin system also reduced the failure rate of electrical cardioversion and the recurrence of AF after electrical cardioversion (Kalus *et al.* 2006).

Antagonism of the TGF-ß$_1$ pathway

Recent research has focused on modification of the TGF-ß$_1$ pathway as a way to possible AF prevention or treatment. In pressure-overloaded rats, the administration of TGF-ß$_1$ monoclonal antibodies prevented atrial fibrosis and diastolic dysfunction (Kuwahara *et al.* 2002). Koyanagi *et al.* (2000) found that anti-TGF-ß$_1$ monoclonal antibodies prevented inflammatory changes by blocking the migration of monocytes in rat hearts and the recruitment of fibroblasts. Dogs with pacing-induced heart failure treated with the antifibrotic drug pirfenidone (a drug-reducing TGF-ß$_1$ expression) had significant reduction in atrial remodeling and AF vulnerability (Lee *et al.* 2006). These favorable effects were associated with reduction in TGF-ß$_1$ expression and atrial fibrosis.

Another promising antifibrotic agent is relaxin, a hormone responsible for extensive changes of the extracellular matrix in the female reproductive system during pregnancy. Both ventricular and atrial cells express receptors for relaxin. Relaxin attenuates expression of TGF-ß$_1$ and its effects on fibroblast differentiation and matrix synthesis (Samuel *et al.* 2007). Whether relaxin might be useful for amelioration of AF substrate is still unknown.

Statins and antioxidants

Statins have anti-inflammatory and anti-oxidant effects; therefore, they might have a potentially beneficial effect on AF. In a canine atrial tachypacing model, simvastatin attenuated the promotion of AF (Shiroshita-Takeshita *et al.* 2007). In another study, Amar *et al.* (2005) demonstrated the beneficial effect of statins in patients after non-cardiac thoracic surgery. Preoperative statin administration was associated with a threefold decrease in the odds of developing AF independently of the change of CRP or interleukin-6.

Beneficial effects on AF occurrence were also documented using ascorbic acid. Oral ascorbic acid administration in patients with persistent AF reduced early recurrence of AF after cardioversion (Korantzopoulos *et al.* 2005).

Corticosteroids

In an animal model of sterile pericarditis, prednisone therapy reduced the incidence of AF (Shiroshita-Takeshita *et al.* 2006). In humans after successful cardioversion of AF, methylprednisolone (16 mg for 4 weeks tapering to 4 mg for 4 months) reduced AF recurrence from 50 % in the control group to 9.6 % in the glucocorticoid group (Dernellis and Panaretou 2004).

Recently, a double-blind, randomized, multicentre Finnish trial (Halonen *et al.* 2007) demonstrated favorable

effect of steroids on post-operative patients without prior AF or flutter, undergoing their first on-pump cardiac surgery, who were randomly subjected to glucocorticoid therapy with hydrocortisone or placebo. The incidence of post-operative AF during the first 84 h was significantly lower in the hydrocortisone group (30 %) than in the placebo group (48 %, p=0.01), without increasing the rates of wound infection or other major complications. These results certainly support the causative role of inflammation in paroxysmal AF, but whether corticosteroids may offer obvious clinical benefit in the perioperative management of cardiac patients will need further study.

Conclusions

The origin and persistence of AF result from a complex interaction between triggers, substrate, and factors involved in atrial remodeling. It is obvious that the pathophysiology of AF differs from one patient to another, but recent advances have helped us to understand more about involved mechanisms and to translate this knowledge into improvements of AF therapy. An example could be the elimination of triggers within pulmonary veins by means of catheter ablation. Dealing with structural atrial remodeling and atrial fibrosis remains still a great challenge. Solving these problems could help us to develop new approaches to AF prevention and treatment.

Conflict of Interest

There is no conflict of interest.

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