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State of the Art Review

Atrial Fibrillation: Basic Mechanisms, Remodeling and Triggers

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Introduction

Atrial fibrillation (AF) is the most common and troublesome arrhythmia in clinical practice and is a significant contributor to cardiovascular morbidity and possibly mortality [1,2]. Although AF can clearly occur in patients without evident heart disease (so-called lone AF), organic heart diseases, such as congestive heart failure (CHF), mitral valve disease, and coronary artery disease, are major co-existing conditions that contribute to the occurrence and persistence of AF. The mechanisms by which these cardiac conditions favor the occurrence of AF are interesting and may help in designing more effective therapeutic approaches. Despite the fact that the pathophysiology of AF has been investigated extensively for almost a century, the underlying mechanisms remain incompletely understood [3].

Classical mechanisms of AF first described in the early 20th century [3] still form the framework for our understanding of its pathophysiology. However, numerous studies performed over the past 10 years have given us more detailed insights into the pathogenesis of clinically-relevant AF. This article reviews the contributions of some of this recent work to our understanding of electrophysiological, ionic and molecular mechanisms of AF and of its clinical pathophysiology and management.

Classical Theories of AF Mechanism

In 1924, Garrey [4] reviewed the contemporary understanding of AF mechanisms, highlighting 3 competing theories of its electrical basis: (1) a "hyperectopia theory", according to which single or multiple rapidly-firing atrial ectopic foci lead to fibrillation (Fig. 1A), (2) a single rotor ("mother wave") with fibrillatory conduction (Fig. 1B), and (3) multiple circuit reentry (Fig. 1C). Moe developed the "multiple wavelet hypothesis" of AF, which resembled earlier conceptualizations of multiple circuit reentry, refining them by replacing the notion of closed loop reentry with the idea that AF is characterized by a large number of propagating wave fronts, a sufficient number of which must always find excitable tissue for the arrhythmia to persist. His concept was solidified by the development of a computer model of atrial tissue, which showed that AF can be sustained by multiple propagating wave fronts if appropriately short and heterogeneous refractory properties are included [5]. Subsequently, experimental work by Allessie et al. provided experimental support for the multiple wavelet model [6].

A general conceptual model of these AF mechanisms is presented in Figure 2. Reentry that maintains AF requires an appropriate substrate and an initiating factor, or trigger, generally in the form of a premature beat. Ectopic activity can provide the trigger for initiating reentry, or if it is rapid and sustained, may maintain AF by itself. In order to explain the irregular atrial activation inherent to AF on the basis of regularly discharging sources like rapid single-site ectopy or single-circuit reentry, one must invoke break-up of the emanating wave front against tissue with spatially variable refractory or conduction properties.

The "wavelength" is a useful concept in the consideration of reentry and AF. The wavelength (distance traveled by the electrical impulse in one

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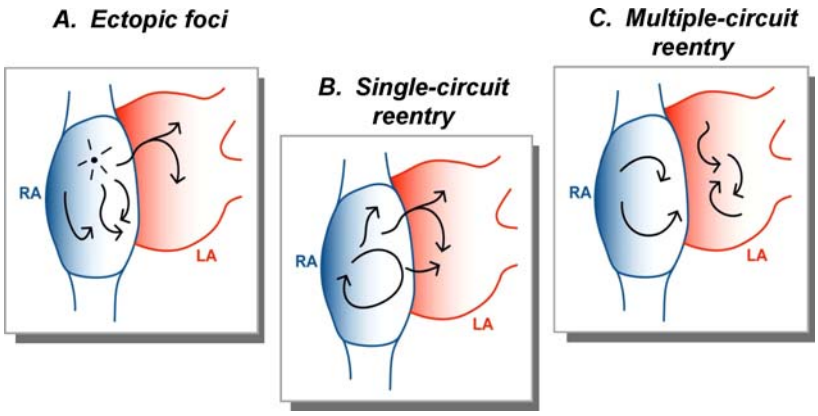

Fig. 1. *Ideas of AF mechanisms in the early 20th century.*

refractory period, or product of refractory period and conduction velocity) is, according to Allessie's leading circle model of reentry, the minimum path length for a reentry circuit (Fig. 3A). It is believed that in normal human atria, the wavelength is such that few reentry circuits can be accommodated and AF, once initiated, tends to terminate spontaneously when the underlying functional circuits die out (Fig. 3B, left). A decreased wavelength permits a larger number of functional reentry circuits to be accommodated within a given mass of tissue, and therefore promotes multiple circuit reentry (Fig. 3B, right).

Recent work suggests that local conduction disturbances (for example, due to tissue fibrosis) can stabilize reentry by producing conduction barriers (Fig. 4), allowing for AF without decreases in wavelength [7]. Haïssaguere et al. have also demonstrated that ectopic activity in the atrial sleeves surrounding pulmonary veins may be crucial in initiating, and possibly even maintaining, AF in some clinical populations [8], consistent with classical "hyperectopia theory".

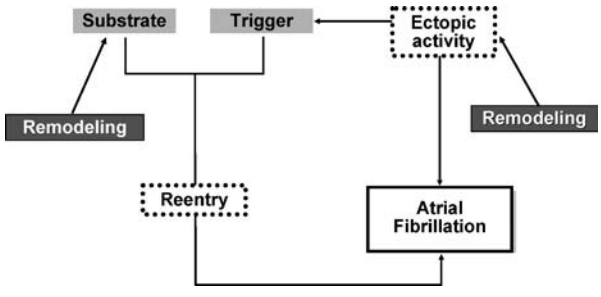

Fig. 2. *A general schema of the mechanisms presently believed to be involved in the pathophysiology of AF.*

Atrial Remodeling

Atrial remodeling refers to any change in atrial structure or function that promotes atrial arrhythmogenesis. Two principal forms have been identified in animal models- tachycardia-induced remodeling and structural remodeling.

Atrial Tachycardia Remodeling

General Properties. Clinical experience suggests that paroxysmal AF often progresses into persistent AF, and the longer AF persists, the more difficult it becomes to maintain sinus rhythm after cardioversion. In 1995, Wijffels et al. made the now-classical observation that AF modifies atrial properties so that AF maintains itself more readily, a phenomenon called electrical remodeling and described as "AF begets AF" [9]. Sustained atrial tachycardia produces a similar form of remodeling, suggesting that it is the rapid atrial rate of AF that is the primary remodeling stimulus [10–12]. The remodeling produced by atrial tachycardia and AF has been termed "atrial tachycardia remodeling" to differentiate it from other forms of atrial remodeling [3]. A prominent finding in atrial tachycardia remodeling is a decrease in atrial effective refractory period (ERP) and reduction in physiological ERP rate adaptation [9–12]. This ERP decrease reduces the wavelength, and thus atrial tachycardia remodeling produces a substrate favorable for AF (Figs. 2 and 3).

The signal transduction leading to ERP abbreviation in AF is still unclear. However, cellular Ca^{2+} loading is believed to play an important role [13]. Ca^{2+} enters the cell through L-type Ca^{2+} channels during each action potential, and with the approximately 10-fold increase in atrial firing rate when the atria go from sinus rhythm to AF, Ca^{2+} loading is substantially enhanced (Fig. 5). Atrial myocytes protect themselves against Ca^{2+}

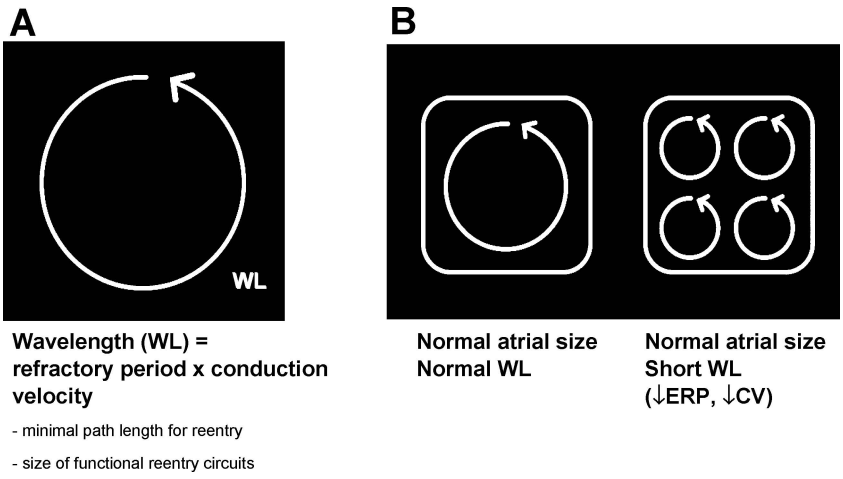

Fig. 3. *(A) The wavelength is given by the product of ERP and conduction velocity. According to leading circle recently theory, the wavelength is the shortest circuit size that can sustain reentry. (B) Left: in a normal atrium with normal wavelength, the number of re-entrant waves is small, thus AF is unstable and self-terminating. Right: if the wavelength is reduced, either by decreasing ERP or conduction velocity (CV), re-entrant circuits are smaller so that more re-entrant waves can be accommodated and AF is more likely to be sustained.*

loading by short- and long-term mechanisms, with the short term mechanisms consisting primarily of functional L-type Ca^{2+} current (I_{CaL}) inactivation and the long-term mechanisms including down regulation of mRNA encoding L-type Ca^{2+} channels [14] and causing sustained I_{CaL} decreases that reduce atrial action potential duration (APD) and consequently ERP [15]. Na^{+} current also appears to be down-regulated [16], potentially contributing to atrial conduction slowing [12,16] and helping to promote AF by reducing the wavelength. In addition to decreasing ERP in an absolute fashion, atrial tachycardia decreases ERP in a spatially heterogeneous way [12,17], which facilitates multiple circuit reentry [5,18]. However, the time course of AF promotion due to atrial tachycardia remodeling is slower than that of ERP changes, indicating the involvement of additional mechanisms [9,12].

Possible factors involved in the time-frame discordance between ERP abbreviation and AF promotion may be slowly-progressive conduction slowing due to slowly-progressive decrease in Na^{+} current (I_{Na}) [12,16], spatially heterogeneous downregulation of the expression of atrial connexin 40 [19,20] and atrial cardiomyocyte

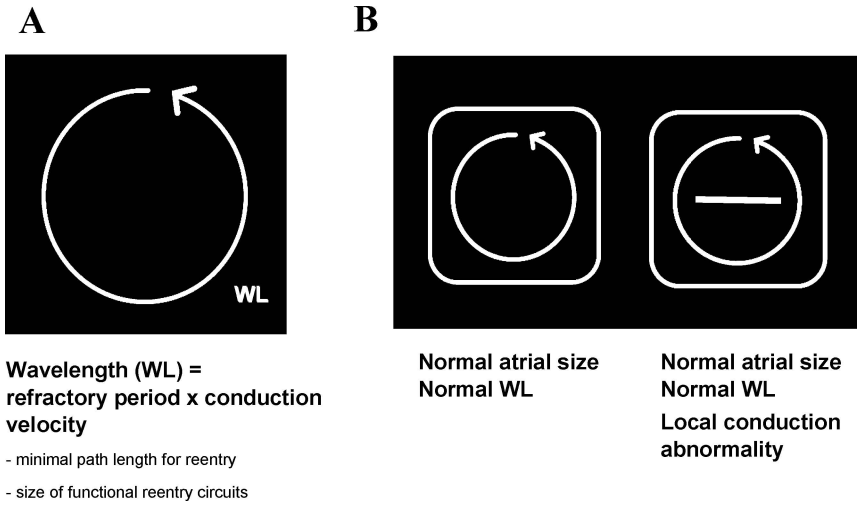

Fig. 4. *Same format as Figure 3. Even without a decrease in wavelength, local conduction abnormalities can stabilize reentry, allowing it to be sustained even when the number of circuits that can be accommodated is small.*

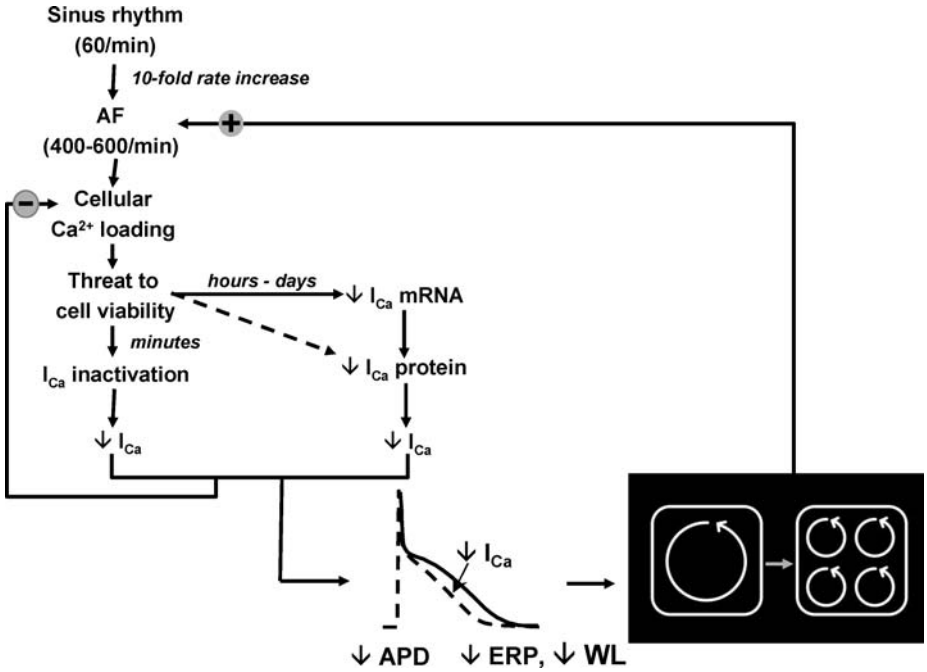

Fig. 5. *A schema of the potential pathogenesis of atrial-tachycardia remodeling. Ca^{2+} loading due to increased rates causes a threat to cell viability, which is prevented by short- and long-term adaptations that reduce Ca^{2+} entry, providing protective negative feedback on Ca^{2+} loading, APD abbreviation, and positive feedback on AF likelihood by reducing ERP and wavelength (WL).*

dedifferentiation [21]. In addition to its electrical effects, atrial tachycardia suppresses atrial myocyte contractility, at least in part by altering Ca^{2+} homeostasis [22], and thereby causes "contractile remodeling" [23] that may contribute to atrial stasis and the associated thromboembolic predisposition, as well as to AF perpetuation. Although the electrical changes caused by atrial tachycardia are rapidly reversible (within several days) after the cessation of atrial tachycardia, other alterations (such as ultrastructural remodeling) may reverse more slowly [21]. Atrial tachycardia remodeling is believed to contribute to a variety of clinically important phenomena, including the tendency of paroxysmal AF to become persistent, the tendency of AF to recur soon after cardioversion, and the tendency for longer-lasting AF to become refractory to pharmacological cardioversion [24].

Ionic Mechanisms. The ERP abbreviation caused by atrial tachycardia remodeling is due to APD abbreviation [15,25]. An important underlying ionic mechanism is down-regulation of I_{CaL} [14], which may contribute to atrial contractile dysfunction [22,23]. There is also evidence for down regulation of the transient outward K^+-current I_{to} [14,15], but its functional importance is unknown. Although initial experimental studies suggested no change in inward-rectifier current in atrial tachycardia remodeling [14,15], recent studies have shown up-regulation of inward rectifier K^+-current [26,27], which may include contributions from both the background K^+ current I_{K1} [26] and a constitutively-activated acetylcholine-dependent current (I_{KACh}) [27]. There is also evidence for decreased I_{Na} [16,28], which may contribute to tachycardia-induced conduction slowing. Atrial myocytes from right atrial appendages of patients with persistent AF have reduced I_{to} [29,30] and I_{CaL} [30,31] and increased inward-rectifier K^+-currents [29,30,32]. To date, decreased I_{Na} has not been documented in cardiomyocytes from AF patients. As in studies with atrial-tachycardia remodeled canine cardiomyocytes [14], inhibition of I_{CaL} mimics the action potential duration changes associated with AF in man [30,31].

Molecular Mechanisms. The molecular mechanisms underlying atrial tachycardia remodeling are still incompletely understood. A conceptual model of atrial tachycardia remodeling is summarized in Figure 5. AF increases atrial rate ~10-fold, which increases atrial myocyte Ca^{2+} loading [13,33]. Since Ca^{2+} loading can be cytotoxic, there is a need for mechanisms to protect against cellular Ca^{2+} overload. Both short and long term mechanisms come into play. Abrupt rate increases

inactivate I_{CaL} within minutes by a combination of intracellular Ca^{2+}-dependent inactivation and incomplete recovery from classical voltage- and time-dependent inactivation [34]. Over the subsequent days to weeks, the expression of mRNA encoding the α-subunits of I_{to}, I_{Ca} and I_{Na} channels decreases in parallel with reductions in ionic currents [14–16]. There is evidence in an isolated mouse atrial cell-line system (HL-1 cells) that excessively rapid activation can downregulate protein expression directly by activating proteases like calpain [35]. Activated myocardial proteases, including calpain and caspases, may directly break down ion channel proteins (like I_{CaL}) and myofilament proteins [36–39], contributing to ion-channel downregulation but also causing myolysis and energy-sparing reductions in contractility. Similar changes (down-regulation of ion-channel mRNA and calpain activation) have been reported in atrial tissue specimens from AF patients [40–43].

Decreased I_{CaL} reduces Ca^{2+} transport into the cell and reduces cellular Ca^{2+} loading, but also decreases action potential duration (I_{CaL} is the main inward current maintaining the action potential plateau), thus decreasing the ERP and wavelength, favoring multiple circuit reentry. There is evidence that reduction in extracellular Ca^{2+} or prevention of Ca^{2+} entry can inhibit some of the remodeling changes caused by atrial tachycardia [33]. The relationship between Ca^{2+} loading and other ionic changes that have been reported with tachycardia-remodeling, such as decreased I_{to} or I_{Na}, changes in connexin expression and increased inward-rectifier currents, is unknown.

CHF and Atrial Structural Remodeling

CHF is one of the most common clinical causes of AF [44]. In a dog model of CHF caused by ventricular tachypacing for 2–5 weeks, the ability to induce prolonged AF duration is markedly increased [7,45,46]. Atrial ERP is unchanged or increased by CHF, but local atrial conduction abnormalities occur in association with marked fibrosis between and within atrial muscle bundles [7]. It is believed that these abnormalities in atrial structure and local conduction may stabilize atrial reentry, allowing for AF-sustaining reentry circuits that sometimes appear to have a stable macro-reentry pattern [47,48]. This mechanism of AF maintenance resembles in some respects the single-circuit reentry AF mechanism championed by Sir Thomas Lewis (Fig. 1B). According to this idea, instead of AF being maintained by multiple simultaneous reentry circuits by virtue of wavelength reduction, wavelength is unchanged but reentry is stabilized by anchoring to fibrotic zones of conduction impairment (Fig. 4).

An additional mechanism that may contribute to atrial tachyarrhythmias in CHF is triggered ectopic activity related to delayed afterdepolarizations that cause focal atrial tachyarrhythmias [49,50], analogous to the mechanism shown in Figure 1A.

Ionic Mechanisms. Like atrial tachycardia, CHF causes remodeling of atrial ionic current and transport mechanisms [51]. However, the ionic remodeling caused by CHF involves a more balanced decrease in the inward current I_{CaL} and outward currents like I_{to} and I_{Ks} [51], resulting in no change or an increase in APD. Thus, the ionic current changes in CHF do not alter atrial action potential properties in a way that favors atrial reentry. On the other hand, CHF also upregulates the Na^+, Ca^{2+}-exchanger (NCX) [51]. The function of the NCX is illustrated in Figure 6A. Ca^{2+} enters the cell during the plateau of the action potential, triggering cellular contraction. This Ca^{2+} then has to be extruded in diastole to maintain ionic balance, with one of the major extrusion mechanisms being the NCX. The NCX extrudes one Ca^{2+} ion for every 3 Na^+ ions transported into the cell, thus carrying a net positive charge into the cell (and tending to depolarize it) with each cycle. If NCX activity is enhanced as in CHF (Fig. 6B), the inward positive-charge carrying function of the NCX is enhanced, potentially producing measurable delayed afterdepolarizations (DADs). If the DADs are large enough,

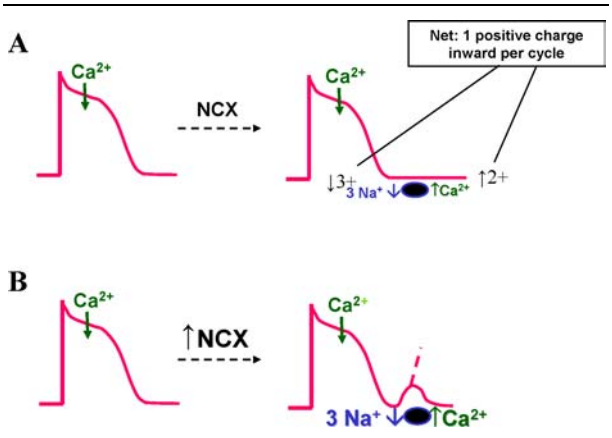

Fig. 6. *(A) The Na^+, Ca^{2+} exchanger (NCX) extrudes Ca^{2+} that enters during the plateau of the action potential by exchanging one Ca^{2+} ion (net charge +2) for 3 Na^+ ions (net charge +3, leading to one extra positive charge moving inward per cycle) during phase 4 (after repolarization). (B) Increased NCX activity due to CHF can increase the net inward charge movement to the point that a perceptible depolarization (a delayed after-depolarization, DAD) results. If the DAD is large enough, it can reach threshold (dashed line) and cause ectopic activity. A sequence of DADs can cause a tachyarrhythmia.*

they can reach threshold and cause ectopic firing and tachyarrhythmias. DAD-related activity may account for the occurrence of focal atrial tachyarrhythmias in experimental CHF [49,50]. Observations of changes in atrial remodeling following recovery from tachypacing-induced CHF in the dog indicate that AF is still inducible when NCX enhancement has disappeared, indicating that ionic remodeling is not essential for CHF-induced AF promotion [46]. On the other hand, atrial fibrosis does not regress following recovery from CHF [45,46], suggesting that fibrosis may be a very important contributor to CHF induced AF promotion.

Molecular Mechanisms. The molecular mechanisms underlying atrial remodeling in CHF are complex. Atrial angiotensin-II (Ang-II) concentrations increase rapidly in dogs subjected to ventricular-tachypacing that induces CHF, in association with increased phosphorylation of the mitogen-activated protein kinases (MAPKs) extracellular signal-related kinase (ERK), p38 kinase and N-terminal-c-jun kinase (JNK) [52,53]. Atrial Ang-II concentrations increase before plasma levels rise [53], suggesting in situ cardiac tissue synthesis as the source of atrial Ang-II increases. Increased tissue Ang-II and phosphorylated MAPK concentrations are followed by an increase in the ratio of pro-apoptotic (Bax) to anti-apoptotic (Bcl-2) protein expression, activation of the apoptotic executioner serine-protease caspase-3, evidence of transient apoptosis (increased terminal dUTP nick-end labeling (TUNEL) positivity and DNA fragmentation), an increased rate of cell death and leukocyte infiltration, and finally tissue fibrosis [53]. The early activation of Ang-II and its known ability to produce many of the changes detected (apoptosis, MAPK activation, necrosis, leukocyte infiltration, fibrosis) suggests that inhibiting Ang-II production or Ang-II interaction with its receptor should be able to prevent this type of remodeling. In fact, ACE inhibition [52,53] and blockade of Ang-II type 1 receptors [54] are capable of preventing atrial structural remodeling and AF promotion in dog models of ventricular tachycardiomyopathy. On the other hand, although ACE inhibition prevents ERK phosphorylation and apoptotic cell death, it does not prevent early JNK and p38 phosphorylation, nor does it significantly reduce the total rate of cell death [53]. Furthermore, the attenuation of atrial fibrosis is only partial, suggesting the involvement of other pathways [53]. The lack of effect of enalapril on total cell death, despite its great effectiveness in preventing apoptosis in this model, suggests that a major portion of cell death is due to other mechanisms such as necrosis.

Atrial fibrotic remodeling is much more prominent than that at the ventricular level in tachypacing-induced CHF [55]. One factor that may be implicated is activation of transforming growth factor $\beta 1$ (TGF$\beta 1$), which occurs at the atrial, but not ventricular, level in tachypacing-induced CHF [55]. This observation is interesting in light of the finding that transgenic mice with constitutively-activated TGF$\beta 1$ have atrial-restricted fibrosis and an AF predisposition in the absence of changes in atrial action potentials or dimensions [56]. Other extracellular matrix proteins that seem importantly altered in atrial structural remodeling include matrix metalloproteinases and their tissue inhibitor [57,58].

Other Recent Remodeling Paradigms

Several novel, clinically-relevant experimental remodeling paradigms have been reported recently. Chronic mitral regurgitation produces a substrate that can sustain AF [59], in association with atrial conduction abnormalities that do not occur with atrial tachycardia remodeling [60] and are in some ways similar to those occurring in CHF [7]. Chronic atrioventricular block and ventricular pacing at physiological rates also promotes AF in association with local conduction abnormalities and mild atrial dilation [61]. This observation may be relevant to the increased incidence of AF in patients with ventricular demand pacemakers [62]. Finally, a recent study has shown that atrial volume overload caused by an aorto-pulmonary shunt in sheep produces a variety of electrophysiological abnormalities, as well as atrial dilation and an AF predisposition [63].

Triggers

Atrial Ectopic Activity and Pulmonary Veins: Experimental Evidence Regarding Electrophysiological Properties of Pulmonary Veins and Potential Role

The cardiomyocyte sleeves of pulmonary veins (PVs) are known to be an important source of ectopic focal activity that initiates and may maintain AF in man [8,64]. A variety of experimental work has been performed to clarify the mechanisms by which PVs may contribute to AF. Chen et al. have demonstrated specific arrhythmic cellular electrical properties, including pacemaker function and a predilection to early afterdepolarizations (EADs) and DADs in PV cardiomyocytes [65]. They have also shown the enhancement of such arrhythmic activity in arrhythmogenic contexts such as chronic atrial tachypacing and thyroid hormone exposure [66,67]. However, other groups have failed to show such primary

arrhythmic activity in intact PV preparations from normal canine hearts [68–70] and hearts of the dogs subjected to 1 week of atrial tachycardia [71]. Exposure to low doses of ryanodine promotes pacing-induced repetitive activity in PV cardiomyocytes, and this activity can be suppressed by Ca^{2+} depletion and NCX inhibition, and enhanced by β-adrenergic stimulation [72]. These observations point to Ca^{2+} release/DAD related mechanisms, suggesting possible arrhythmogenic abnormalities in Ca^{2+}-handling in PV cardiomyocytes.

Other observations suggest a possible contribution of reentry in or near the PVs to AF. The cardiomyocyte-sleeve fiber orientation in PVs shows abrupt transitions from longitudinal to transverse alignment, producing a predilection to localized conduction slowing, particularly for premature activations [68,73]. In combination with PV cellular properties (reduced resting potential, phase 0 Na^+-current and action potential duration) that would be expected to reduce the wavelength [69], these anatomical properties could make the PVs a favored site for atrial reentry. Indeed, optical mapping has shown PV reentry in normal dogs [74] and points to PV reentry as a source of rapid activity during AF in acutely dilated sheep atria [75]. Recent clinical observations also point to a significant role for PV reentry in AF [76].

Remodeling and Triggers

Much of the work on atrial remodeling has focused on its ability to promote reentry. However, there is intriguing information which suggests that remodeling may also promote ectopic activity, as shown in Figure 2. In AF associated with either CHF or atrial tachycardia remodeling paradigms, rapid activation with a focal pattern has been demonstrated in PV sleeves [77,78]. As mentioned above, atrial NCX activity is enhanced in CHF [51], providing a potential basis for triggered activity-related tachyarrhythmias [49,50]. PV cardiomyocytes from dogs with atrial-tachycardia remodeling have been shown to demonstrate a variety of forms of abnormal spontaneous activity [66], although this has not been confirmed in other studies [71]. Radiofrequency ablation of the thoracic veins can suppress AF in dogs with chronic AF [79], but surgical excision of the PVs does not affect atrial tachyarrhythmias in isolated left atrial-PV preparations from dogs subjected to 7 day tachycardia remodeling [71]. The discrepancy may be due to significant tissue destruction outside the PVs with radiofrequency thoracic vein ablation [79], to technical differences, or to the shorter duration of remodeling in the isolated-preparation study [71].

Therapeutic Implications of Atrial Remodeling

Pharmacological Prevention of Atrial Tachycardia Remodeling

Atrial tachycardia remodeling has a variety of potentially deleterious clinical consequences and its prevention is a potentially attractive therapeutic approach [3,24]. Early enthusiasm about the value of I_{CaL} blockers in preventing tachycardia-remodeling [80] was tempered by subsequent studies showing that L-type Ca^{2+}-channel blockers are ineffective for remodeling caused by >24 hours of tachycardia [81,82]. Clinical studies of I_{CaL} blockers have produced variable results, with the consensus supporting lack of efficacy [83]. Similarly, early reports of efficacy of a Na^+,H^+-exchange inhibitor and of renin-angiotensin system inhibition on short-term atrial tachycardia remodeling [84,85] were also followed by negative results with longer-term (>24-hour) paradigms [86,87], pointing out the limitations of short-term studies. Several drugs have been shown to prevent experimental atrial remodeling due to atrial tachycardia longer than several days. For example, mibefradil, a Ca^{2+}-channel blocker selective for T-type channels, prevents remodeling due to 7 days of atrial tachycardia in dogs [81,88], but is no longer available on the market. The superior therapeutic efficacy of amiodarone in preventing AF in tachycardia-remodeled canine atria appears to be due to prevention of tachycardia-remodeling [89], which may contribute to its superior clinical efficacy for the arrhythmia [90]. Like mibefradil, amiodarone also has T-type Ca^{2+}-channel blocking action [89], but both compounds have many other effects including potential Na^+-channel blockade, K^+-channel blockade, metabolic effects, etc (discussed in detail in reference 83), so that the precise mechanism of their remodeling-prevention efficacy requires further study.

Recently, evidence for increased oxidative stress has been obtained in atrial tissue samples from AF patients [91] and from dogs subjected to atrial tachycardia [92]. Carnes et al. found the antioxidant vitamin ascorbic acid to be protective against atrial tachycardia remodeling up to 48 hrs in dogs [92]. Although a subsequent study failed to confirm a protective effect of ascorbate [93], other antioxidant molecules, such as probucol and oxypurinol, seem to have some ability to suppress tachycardia-remodeling [94].

Chung et al. reported that the inflammatory marker C-reactive protein (CRP) is elevated in AF patients and that higher CRP levels are observed in persistent than paroxysmal AF [95]. The same group subsequently demonstrated that

CRP levels are not only higher in current AF patients, but may also predict the future development of AF [96]. These observations suggest a potential pathophysiological role of inflammation in AF development. Prednisone, with strong anti-inflammatory properties, has been shown to prevent atrial tachycardia remodeling-induced AF promotion in dogs [97]. In addition, a relatively small-scale clinical trial showed that low-dose methylprednisolone prevents AF recurrence, while lowering CRP concentrations [98].

Simvastatin has both anti-oxidant and anti-inflammatory properties, and has been shown to suppress atrial refractoriness abbreviation, arrhythmia promotion and L-type Ca^{2+}-channel α1c subunit protein downregulation in dogs exposed to 7-day atrial tachycardia at 400/min [93]. Statins have been found to protect against clinical AF in some retrospective studies [99,100], but a prospective trial of pravastatin for prevention of AF recurrence after cardioversion in persistent AF patients failed to show benefit [101]. If statins were effective in preventing AF recurrence, they might constitute a safe and useful addition to the clinical armamentarium, but current clinical evidence is insufficiently supportive.

Suppression of Atrial Structural Remodeling

ACE inhibitors [52,53] and Ang-II receptor antagonists [54] have shown value in the prevention of CHF-related arrhythmogenic atrial structural remodeling in dogs. Clinical studies have confirmed that ACE inhibition prevents AF in patients with left ventricular dysfunction [102,103] and hypertension [104,105]. The evidence that enalapril produces incomplete attenuation of the atrial remodeling response in CHF [53] suggests that further work is needed to identify additional and/or more effective molecular targets for the prevention of atrial structural remodeling. In addition, there are data which suggest that inhibiting renin-angiotensin signaling may prevent AF recurrence in patients without signs of LV hypertrophy or dysfunction [106,107], so further work is needed to clarify the indications, mechanisms and utility of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in AF.

Effects of Atrial Remodeling on the Response to Antiarrhythmic Drugs

The importance of AF duration as a determinant of antiarrhythmic drug efficacy has long been recognized [108]. Recent work suggests that atrial remodeling may be an important determinant of the AF response to antiarrhythmic drug therapy. Realistic ionically-based mathematical modeling indicates that atrial tachycardia remodeling should reduce the response to I_{Kr}-blocking drugs by abbreviating and triangularizing the action potential, such that the I_{Kr} contribution to repolarization is minimized [109]. Correspondingly, the I_{Kr} blocker dofetilide is much less effective in AF in a tachycardia-remodeled substrate than in a CHF-related structurally remodeled substrate [110]. Dofetilide's effects on refractoriness are decreased in AF-remodeled goat atria, and dofetilide and ibutilide are much less successful in converting AF in the tachycardia-remodeled atrium than AVE-0118, which acts on K^+-currents other than I_{Kr} [111]. In addition, there is evidence that the efficacy of Na^+-channel blockers is also reduced with atrial-tachycardia remodeling [112], possibly because of reduced state-dependent I_{Na} blockade during the abbreviated remodeled action potential plateau.

Model Considerations

This article has focused primarily on results from experimental models of AF and their clinical relevance. Experimental models and clinical studies have different strengths and weaknesses and provide complementary information. In experimental studies, specific variables can be isolated and studied precisely. Clinical studies, particularly experimental analyses based on tissue samples, are always limited by a large number of variables that are inherently poorly controllable (e.g., inter-patient differences in underlying cardiac disease, drug therapy, arrhythmia type and duration, etc.). On the other hand, the applicability of experimental models to specific clinical populations is always an issue. For example, animal studies of atrial remodeling for up to 6 weeks show that NCX expression is upregulated in CHF-related structural remodeling [51] but not altered by atrial tachycardia [14]. Schotten et al. showed that patients with long-standing (>3 months) AF and mitral valve disease have NCX upregulation compared to a sinus-rhythm control group [23]. The hemodynamics of the 2 groups were similar, suggesting that NCX up-regulation was not due to cardiac dysfunction, and possibly that long-standing AF in man leads to NCX upregulation, unlike 6-week atrial tachycardia in animals. On the other hand, drug therapy was quite different between AF and sinus-rhythm patients [23]. This and other potential differences could have contributed to NCX up-regulation. Therefore, further experimental and clinical research is needed to determine the precise determinants of NCX upregulation in AF.

The interplay between experimental and clinical investigations is particularly important

for the rapidly-developing field of AF genetics. Although a familial predisposition to AF has been noted for a long time [113], only recently have modern genetic studies allowed the site of gene variations involved in familial AF to be identified [114–117]. Three of these have been shown by expression studies in heterologous systems to involve gain-of-function mutations in K^+-channels [115–118], which would be expected to accelerate atrial repolarization and promote multiple-circuit reentry [3]. The challenging nature of this type of work is illustrated by the fact that the mechanistic basis for the first familial AF form to be linked genetically remains elusive eight years later [114]. While familial AF is rare, genetic predisposition to the arrhythmia may be much more common [118]. At least one factor leading to AF predisposition may be a polymorphism in the promoter region of the connexin 40 gene that leads to decreased transcription of connexin 40 message [119], in agreement with the putative role of connexin 40 downregulation in atrial tachycardia remodeling [19,20] and the results of connexin 40 knockout studies in mice [120]. Polymorphisms in ion channels may also contribute to a predisposition to AF, with one study have suggesting a role for a polymorphism in the I_{Ks} accessory subunit minK [121]. However, the AF-promoting minK isoform appears to be associated with reduced I_{Ks} upon co-expression with the I_{Ks} pore-forming subunit KvLQT1, raising questions about the association and/or pathophysiology [122].

Conclusions

Recent research has provided novel insights into the mechanisms and role of remodeling and triggers in AF pathophysiology. These insights have already been translated into improvements in AF therapy, and promise to lead to continued therapeutic innovations in the future. Particularly important unsolved mysteries that remain to be addressed include the mechanistic basis for the privileged role of the pulmonary veins in AF, the genetic factors that determine AF susceptibility and the signal transduction mechanisms involved in profibrillatory atrial remodeling. Developments in genomics, molecular genetics, proteomics and cell biology should allow for major advances in these areas, which will both increase our knowledge and allow for the identification of new approaches to treatment.

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