Review

Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management?

Stanley Nattel a,b,c,*

a Department of Medicine and Research Center, Montreal Heart Institute, 5000 Belanger Street E., Montreal, Quebec, Canada H1T 1C8
b Department of Medicine, University of Montreal, Montreal, Quebec, Canada
c Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

Received 26 September 2001; accepted 26 November 2001

Abstract

Atrial fibrillation (AF) is a very common clinical problem, and presently available treatment options are suboptimal. A tremendous amount has been learned over the past 10 years about the atrial substrates that support and maintain AF. This understanding of the fundamental mechanisms underlying AF has opened up a variety of new, rationally-based therapeutic approaches. The present paper reviews what is known about the mechanistic substrates that lead to AF and discusses the potential therapeutic consequences. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Antiarrhythmic agents; Arrhythmia (mechanisms); Gene expression; Ion channels; Remodeling

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia. AF is responsible for considerable morbidity and medical costs [1], is a major determinant of stroke [2] and may increase mortality, particularly in patients with congestive heart failure (CHF) [3]. Present therapy of AF is suboptimal. Drugs to maintain sinus rhythm have incomplete efficacy and may increase mortality by causing proarrhythmia [4]. Non-pharmacological therapy of AF is advancing, but is still experimental and will not in the near future be applicable to the majority of AF patients [5].

Over the past 10 years, much has been learned about the substrates that support and maintain AF. This paper will review what is known about AF substrates, will consider the role that understanding AF mechanisms may play in determining therapeutic approaches, and will evaluate potential new avenues opened up by recent insights.

2. Potential basic arrhythmia mechanisms underlying AF

2.1. Historical context

Present concepts about AF mechanisms are rooted in ideas first put forward in the early 20th century, summarized in a detailed review article by Garrey [6] and presented schematically in Fig. 1. Garrey and Mines conceived of multiple functional circuits maintaining AF (Fig. 1A), varying in space and time, and requiring a ‘critical mass’ of tissue for arrhythmia maintenance [6,7]. The opposing notions of single-circuit reentry (Fig. 1B) and ectopic activity (Fig. 1C) with fibrillatory conduction subsequently fell into disfavour. Single-circuit reentry was clearly responsible for atrial flutter [8], and the differences
in behaviour and therapeutic response between atrial flutter and AF made single-circuit reentry an unlikely candidate to underlie AF. Atrial ectopy clearly caused atrial tachycardias, but the efficacy of electrical cardioversion in terminating AF and the infrequency of discrete atrial tachyarrhythmias after AF cardioversion made a role for ectopic foci in AF maintenance seem unlikely. However, atrial ectopy clearly remained potentially important as a trigger for AF initiation and the common association of atrial flutter with AF in many patients, as well as the occurrence of arrhythmias with features of both [9], left open a possible role for atrial ectopy and single-circuit reentry in AF.

2.2. Multiple circuit reentry and therapeutic implications

In his classical computer model [10], Moe refined the notions of Garrey by conceiving of AF as occurring when multiple simultaneous wavelets, fragmented in space and time by atrial electrical heterogeneity, find excitable tissue in their course and maintain continuous electrical activity (the ‘multiple wavelet hypothesis’). AF maintenance is then a probabilistic function governed by the number of wavelets, the size of atrial tissue and the proportion of atrial tissue that is refractory at any time. The determinants of multiple wavelet reentry were made more intuitively understandable by the ‘leading circle’ concept, according to which functional reentry naturally establishes itself in the smallest circuit able to maintain activity [11]. Minimum circuit size is given by the wavelength (product of effective refractory period (ERP) and conduction velocity (CV)), and was shown to determine AF occurrence in a conscious dog model [12].

According to multiple wavelet and leading circle concepts, AF should be more likely if ERPs are short, conduction is slow, or the atria enlarged. These determinants fit with the knowledge that AF is more likely in dilated atria with slowed conduction. The efficacy of antiarrhythmic drugs in AF termination generally parallels their ability to prolong atrial ERP, increase wavelength and increase the size of reentry circuits during AF [13–15]. The success of multiple-circuit reentry in explaining determinants of AF led to its becoming the dominant conceptual framework. The surgical MAZE procedure, the single most effective approach to AF presently available, was developed based on the notion that division of the atria into small functional tissue masses would prevent multiple circuit reentry [16].

2.3. Role of ectopic activity as a mechanism and a target

AF is frequently initiated by atrial premature complexes (APCs) [17]. The ability of APCs to induce AF is related to their timing and location relative to electrical heterogeneity gradients [18–20]. The potential importance of ectopic activity in AF has acquired great significance with the recent recognition of the important role of pulmonary vein ectopy [21]. Pulmonary vein ectopy can trigger reentry in the presence of a vulnerable substrate. It can also cause atrial tachyarrhythmias that lead to multiple-circuit reentry via atrial tachycardia (AT)-induced remodeling (see below). Other sites, including the venae cavae, the ligament of Marshall, and other atrial regions, can also give rise to ectopic activity that plays a role in AF and is amenable to ablation [22–24]. New non-pharmacological approaches to AF directed at eliminating ectopic foci are reviewed elsewhere in this issue [25].

2.4. Single-circuit reentry

Like rapid atrial ectopy, a single atrial reentry circuit can give rise to fibrillation by virtue of fibrillatory conduction. Evidence for this mechanism has been obtained in dogs with CHF [26], and the success of atrial flutter ablation in preventing AF in some patients also points towards potential common mechanisms [27]. Mandapati et al. provided evidence for single microreentrant sources in the
left atrium acting as a dominant generator in AF [28]. Patients with AF and apparent single-circuit macroreentry can be cured by a single linear radiofrequency-ablation lesion [29].

3. Electrical remodeling due to atrial tachycardia—
the genesis of a substrate for multiple-circuit reentry

An important development in the understanding of AF pathophysiology was the demonstration that atrial tachyarrhythmias, both AF and rapid regular atrial tachycardias, alter atrial electrophysiology to promote AF [30,31]. This process has been termed ‘electrical remodeling’ [30], and has potentially important clinical implications [32]. Electrical remodeling may explain why paroxysmal AF tends to become persistent [30], why recurrences of AF often occur early after cardioversion [33], how atrial tachyarrhythmias like reentrant supraventricular tachycardias or atrial flutter can lead to AF and why longer-term AF is resistant to antiarrhythmic drug therapy [32].

3.1. Changes in tissue electrical properties

Atrial tachycardia (AT) decreases atrial ERP and ERP rate-adaptation in experimental models [30–32,34–36]. Conduction slowing occurs in dogs with AT-remodeling [35,36], but not goats [30]. In patients with AF, restoration of sinus rhythm is followed by increases in atrial ERP, normalization of ERP rate-adaptation and evidence of accelerated intra-atrial conduction, implying recovery from remodeling-induced electrophysiological changes similar to those noted in experimental animals [37–41]. AT reduces ERP in a spatially heterogeneous way, with heterogeneity contributing to AF inducibility and maintenance [42]. Changes in conduction develop more slowly than those in ERP [35]. The wavelength decreases, allowing more reentrant waves to be accommodated and promoting multiple circuit reentry [35].

3.2. Underlying cellular and ionic bases

AT reduces ERP by decreasing action potential duration (APD) [43,44]. APD reductions are due primarily to decreased L-type Ca$^{2+}$-current (I$_{Ca,L}$) in both animal models and man [43,45,46]. Even short-term AF (5–15 min) is followed by reduced ERP and increased AF vulnerability [47,48], likely because of voltage- and Ca$^{2+}$-dependent I$_{Ca,L}$ inactivation [49,50]. Longer-term AT decreases I$_{Ca,L}$ by down-regulating pore-forming I$_{Ca,L}$ α-subunits [51]. In addition to decreasing I$_{Ca,L}$, AT decreases transient outward K$^+$-current (I$_{K1}$) [43,45]. There is also evidence for increases in inward-rectifier currents, that could contribute to APD shortening, in patient samples [45,52]. A recent study suggests that conductance of the background inward rectifier I$_{K1}$ is increased by AT, whereas the acetylcholine-activated K$^+$-current is reduced [52].

AT-induced CV reduction in the dog is related to slowly developing decreases in Na$^+$-current (I$_{Na,L}$) [53]. In addition, AT may alter the expression of connexin channels that couple atrial cells, but the nature of connexin changes remains unclear. One group has shown AT to increase connexin43 expression [54], whereas another has shown spatially heterogeneous decreases in connexin40 without change in connexin43 [55,56]. To date, no direct link has been made between AT-related alterations in connexins and conduction changes.

In addition to downregulating I$_{Ca,L}$, AT alters intracellular Ca$^{2+}$ handling [57]. The systolic Ca$^{2+}$-transient is reduced, decreasing contraction strength and contributing to an atrial cardiomyopathic phenotype [57]. AR-related alterations in cellular Ca$^{2+}$-handling likely contribute to changes in APD dynamics in response to changes in firing rate and pattern [58,59]. Cellular ultrastructural remodeling likely also contributes to the atrial cardiomyopathic phenotype associated with AT/AF [60]. Cellular changes consistent with dedifferentiation occur, including cellular myolysis, and may contribute (along with Ca$^{2+}$-handling abnormalities) to the atrial contractile dysfunction occurring after atrial cardioversion [60,61]. Slow development and recovery of such ultrastructural abnormalities may contribute to slowly developing and recovering remodeling-induced changes in the substrate during AF and AT [62]. Atrial dilation may also result from AT [31], and may contribute to AF by activating stretch-operated channels and/or by increasing atrial tissue mass; however, recent studies suggest that AT is a relatively weak stimulus to atrial dilation [63].

3.3. Impact of AT-remodeling

Should AF initially be maintained by other mechanisms like rapid ectopy or single-circuit reentry, AT-remodeling will favour transition to multiple-circuit reentry. Multiple-circuit reentry thus becomes a final common pathway of many cases of AF (Fig. 2), irrespective of the initial mechanism [64]. This transition has been reported clinically, with clear therapeutic consequences [65].

3.4. Signal transduction underlying tachycardia-
remodeling: can it be prevented?

The prevention of AT-remodeling could be an interesting potential target in AF therapy. Although the ionic changes caused by AT-induced remodeling have been studied in detail [66], much less is known about signalling mechanisms leading to ion channel alterations. The effects of verapamil on short-term (<24 h) AT/AF-induced contractile and electrophysiological changes point to a role for Ca$^{2+}$-loading as a signal for remodeling [33,47,48,67,68]. In support of this notion, AT rapidly
Fig. 2. Role of tachycardia-induced remodeling in AF mechanisms.

3.5. Therapeutic implications of AT-remodeling

Longer-duration AF is more resistant to antiarrhythmic drug therapy [32,88]. Underlying mechanisms are unknown. Sustained AF in dogs with AT-remodeling is resistant to dofetilide, whereas AF in CHF dogs is quite sensitive [89]. The decreased sensitivity associated with AT may be due to differences in AP morphology, which determines the contribution of various ionic currents [90] and the state-dependent actions of antiarrhythmic drugs [91], to decreased intrinsic channel sensitivity to blocking actions, or to different basic arrhythmia mechanisms. The ERP-prolonging actions of pilsicainide are reduced by 14-day AT-remodeling, whereas CV-slowing properties are unaltered [92]. More work is needed to understand how AT-remodeling alters antiarrhythmic drug action.

Ionic remodeling may be a potentially interesting target for AF therapy. AT-remodeling promotes AF maintenance, progressively decreasing the chance of spontaneous conversion, and increasing AF recurrence rate after termination. Because of a risk of thromboembolism, patients with AF of >48-h duration are given oral anticoagulants and drugs to control ventricular rate, and cardioverted at least 3 weeks later. During this time, AT-remodeling develops, decreasing the chances of successful cardioversion. Pharmacological conversion of AF often fails, perhaps because of AT-remodeling. A drug that prevents AT-remodeling might be useful to shorten AF paroxysms, to increase the efficacy of pharmacological therapy of recent-onset AF, and to promote the restoration and maintenance of sinus rhythm in patients undergoing electrical cardioversion. Based on the proposed role of Ca\(^{2+}\)-loading in AT-remodeling, Tieleman et al. have suggested that interventions that reduce Ca\(^{2+}\)-loading, like the I\(_{Ca, T}\) antagonist verapamil, may be useful clinically to prevent AT-remodeling [33,93]. Conversely, it has been suggested that digitalis may exaggerate remodeling by promoting Ca\(^{2+}\)-loading [94]. One clinical study has suggested that verapamil therapy may indeed increase the probability of sinus...
rhythm maintenance after cardioversion of AF [95]; however, another study showed no benefit [96] and a third found that the post-cardioversion recurrence rate of AF was the same whether patients were treated with digitalis or verapamil prior to cardioversion [97]. It remains to be determined whether successful clinical approaches to preventing AF-induced remodelling can be developed based on other experimentally identified pharmacological approaches [72,76,87] and to define clinical indications.

Other aspects of the therapeutic approach to AF may also benefit from considering the contribution of remodeling. Since all forms of AT can lead to AT-remodeling and thereby to AF, it is appropriate to search for treatable causes of AT that may underlie AF in specific patients. AV reentrant tachycardias or atrial flutter may lead to AF in some individuals [27,98] and in such cases their control can prevent AF. A corollary of the notion that ‘AF begets AF’ is the idea that ‘sinus rhythm begets sinus rhythm’ [99]. Prompt restoration of sinus rhythm can reverse remodeling-induced changes and may reduce the chances of AF recurrence [100].

4. Atrial remodeling associated with CHF—a substrate for both reentry and ectopic activity

CHF is one of the most common clinical causes of AF, and AF may have a significant impact on the prognosis of CHF patients. Animal models of CHF display increased susceptibility to AF, with electrophysiological changes that differ from those in AT-remodeling [101,102].

4.1. Changes in tissue electrical properties

Unlike AT, CHF does not decrease atrial APD or ERP, on the contrary tending to lengthen them [101,102]. Animal models of CHF suggest no change in global atrial CV, but important rate-sensitive abnormalities in local conduction caused by interstitial fibrosis [102]. In the canine ventricular-tachypacing CHF model, atrial myocytes have normal resting potentials [103]. However, these experimental studies are relatively short-term compared to the time course of clinical CHF. In tissues from patients with severe atrial dilation, atrial APs may be markedly depolarized and show striking abnormalities of phase 0 depolarization, which would be expected to cause substantial conduction slowing [104].

4.2. Ionic remodeling due to CHF

Like AT, CHF causes atrialionic remodeling [103]; however, the nature of ionic changes is different. CHF reduces $I_{Ca,t}$ density to a much lesser extent ($\sim 30\%$) than AT ($\sim 70\%$). Like AT, CHF substantially decreases $I_{Na}$ but unlike AT, which does not affect the delayed-rectifier current ($I_K$), CHF significantly decreases the density of the slow component ($I_{Ks}$). Although 6-week AT does not alter the expression of the $Na^+,Ca^{2+}$-exchanger (NCX) [51], NCX expression is substantially increased by experimental CHF [103].

4.3. Potential mechanisms of AF in CHF

In dogs subjected to AT, AF has the features of multiple-circuit reentry: rapid, irregular electrograms with evidence of multiple reentrant waves on epicardial mapping [35,89]. AF induced in the presence of CHF shows more regular electrogram activity, and often appears to be maintained by a small number of stable reentry circuits [26,64,89]. The greater regularity of electrogram activity in CHF is likely due to the greater ERP, which limits the rate of reentry and number of circuits that can be maintained. Larger ERP values also likely explain the low vulnerability of CHF-remodeled atria to AF induction by single extrasytoles [102]. In the absence of ERP shortening, other changes are required to explain atrial reentry in CHF. CHF causes extensive atrial fibrosis that separates muscle bundles, causing localized conduction abnormalities [102] that may stabilize reentry. CHF may provoke ectopic atrial tachyarrhythmias by increasing NCX activity [103] and causing delayed afterdepolarizations and triggered activity [105,106], inducing AT-remodeling that promotes reentry. Finally, atrial dilation is quite important in CHF [63], potentially promoting AF by increasing tissue mass and stimulating stretch-activated channels.

4.4. Signal transduction in CHF-related AF

Clinical studies show activation of the renin-angiotensin system and mitogen-activated protein kinases (MAPKs), particularly extracellular signal-related protein kinase (ERK), in AF [107,108]. In canine CHF, atrial angiotensin concentrations are increased and MAPKs are activated [109]. Enalapril attenuates these changes, reducing atrial fibrosis and AF promotion [109]. Transient activation of cell-death pathways may also be important in the development of fibrosis [110].

4.5. Implications of CHF-induced atrial remodeling for therapeutics

CHF-related AF is particularly susceptible to termination by class III antiarrhythmic drugs [89], possibly relating to the effectiveness of dofetilide in clinical AF associated with CHF [111]. The prevention of atrial structural remodeling may be useful to prevent development of the AF substrate. The effectiveness of angiotensin antagonism in reducing arrhythmogenic CHF-related atrial remodeling [109] may account for the efficacy of converting-enzyme inhibitors in preventing AF in MI patients with left ventricular dysfunction [112]. Atrial histopathology in other AF-related clinical conditions [113,114] is similar to...
that in experimental CHF, so angiotensin antagonism might have broader applicability in AF therapy. Triggered activity in CHF-related atrial tachyarrhythmias may be targeted by pharmacological therapy and non-pharmacological approaches directed at privileged sites for ectopic activity.

5. Other conditions associated with AF and potential mechanisms

5.1. Thyrotoxicosis

Thyrotoxicosis is a well-recognized cause of AF; however, the detailed pathophysiology of thyrotoxic AF is poorly understood. Atrial APD is decreased by hyperthyroidism [115], which may promote atrial reentry by decreasing ERP. Hyperthyroidism increases I_a and enhances its temperature dependence in rabbit ventricle, but does not affect rabbit atrial I_a [116,117]. Ventricular I_Ca is increased by hyperthyroidism in guinea pigs [118,119] and atrial tissue samples from patients with ‘latent hyperthyroidism’ show increased I_Ca and increased α_1-subunit protein expression [120]. Increased I_Ca could promote AF by contributing to the generation of triggered ectopic activity due to Ca^{2+} overload [121]. Increased levels of sympathetic drive occur with hyperthyroidism [122], potentially contributing to both Ca^{2+}-loading and ERP abbreviation; therefore, beta-adrenoceptor antagonists may be particularly useful in thyrotoxic AF.

5.2. Postoperative AF

AF is a common complication of cardiac surgery, tending to lengthen hospital stay and increase costs. Beta-adrenergic receptor antagonists are particularly effective in postoperative AF [123], suggesting specific mechanisms sensitive to autonomic nervous system function. Little is known about the precise mechanisms involved in postoperative AF. One study suggested that increased I_{CaL} density is a risk factor for postoperative AF [46], pointing to a possible role for Ca^{2+}-overload and related triggered activity [121]. A recent study used retrospective controls to show that patients treated with ascorbic acid had a reduced incidence of postoperative AF, pointing to potential perioperative abnormalities in oxidation-reduction state [87]. This report opens up novel potential approaches to preventing postoperative AF. Pericarditis is likely to be common post-thoracotomy, and experimental pericarditis promotes atrial flutter and fibrillation [124]. There is also evidence for abnormalities in connexin expression in postoperative AF [125], although why these occur and how they promote AF is unknown.

5.3. Other cardiac conditions

A variety of other cardiac conditions, including hypertension, senescence, coronary artery disease and rheumatic valve disease, are associated with AF. The atrial histopathology and AP properties of dogs with mitral valve disease and atrial arrhythmias [126] resemble those in CHF [102], pointing to similar mechanisms. Both aging and rheumatic valve disease are also associated with atrial fibrosis in man [113,114]. A recent study suggests that AF in patients with rheumatic heart disease may begin with organized tachyarrhythmias originating near the coronary sinus os, and that ablation in this region may be effective in arrhythmia suppression [127]. These ATs may be due to triggered activity from cells in the coronary sinus region [128], although an anatomically determined reentry circuit is another possibility. Hypertension may be associated with renin-angiotensin system activation [129], which could lead to fibrotic atrial changes. Alternatively, diastolic dysfunction, increased intra-atrial pressures and atrial hypertrophy/structural remodeling could be involved. The association between AF and coronary artery disease could be due to cardiac hypertrophy and failure related to myocardial dysfunction caused by ischemia and/or infarction, or may be due to more direct consequences of coronary artery disease.

6. Intrinsic determinants of the AF substrate

Sections 3–5 have dealt with how various pathologic states alter cardiac structure and electrical function to create a substrate for AF. Since such changes lie outside normal cardiac function, they may be considered ‘extrinsic’ determinants of the AF substrate. However, these changes are superimposed on the properties of the normal heart, which continue to play a role in governing the occurrence of AF. The structural and ionic properties of the normal atria may thus be considered to constitute ‘intrinsic’ determinants of AF.

6.1. Ionic determinants

A wide variety of ionic currents and transport processes acting in voltage- and time-dependent fashions generate the cardiac action potential [130]. A summary of the intrinsic and extrinsic ionic determinants of AF is presented in Fig. 3. APD (and therefore ERP) is particularly determined by I_{CaL} (which flows during the plateau and tends to keep the cell depolarized) and by repolarizing K^+-currents, which tend to repolarize the cell and terminate the action potential. I_K is a crucial repolarizing current. The rapid component I_{Kr} is a common target for antiarrhythmic drugs in AF. Unfortunately, I_{Kr} is a ubiquitous current and the same drugs that prevent atrial reentry by inhibiting I_{Kr} and prolonging atrial ERP can also excessively prolong ventricular APD and lead to afterdepolarizations and ventricular proarrrhythmia [131]. I_{Kr} likely contributes little to atrial repolarization under normal conditions, but is strongly enhanced by adrenergic stimula-
and may be important in adrenergically sensitive forms of the arrhythmia. \( I_{kur} \) (ultrarapid \( I_k \)) is important in human atrial repolarization [132], is carried by Kv1.5 subunits [133,134] and appears to be absent in human ventricular and Purkinje cell myocytes [134,135]. Because of its strong atrial-selective expression, \( I_{kur} \) is a potential target for atrial-selective antiarrhythmic drugs. Reducing \( I_{af} \) generally decreases APD by raising the plateau and likely to causing increased \( I_k \) activation, but a variety of responses can occur depending on underlying action potential morphology [49,90]. Classical leading circle theory suggests that reduced \( I_{af} \) should slow conduction and promote multiple-circuit AF. On the other hand, recent experimental work suggests that \( I_{af} \) blockers may actually terminate AF while enlarging the excitable gap [136]. Recent theoretical work suggests that \( I_{af} \) blockers suppress spiral wave reentry by reducing excitability, thereby leading to AF termination [137].

The heart possesses a set of ion channels sensitive to cell volume and stretch, including Cl\(^-\) [138], K\(^+\) [139] and non-selective cation [140] channels. Atrial stretch may in itself strongly promote AF [141], presumably in large measure by activating stretch-sensitive channels. Non-selective cation channels may be particularly important in AF associated with atrial dilation, and may be modifiable by specific pharmacological interventions [142]. Atrial myocytes possess the intrinsic pacemaker current \( I_f \) [143]. Modulation of \( I_f \) by autonomic and neurohumoral factors, as well as pathological remodeling, could enhance atrial automaticity and lead to ectopic complexes and tachycardias. Recently developed drugs that suppress automaticity by specifically inhibiting \( I_f \) [144] may prove to be useful tools both to evaluate the potential role of \( I_f \) in atrial ectopic activity involved in AF and, should such a role be established, to treat AF.

6.2. Structural determinants

There has been a tendency to think about the atria as a two-dimensional structure. Gordon Moe’s classical computer model of AF used a flat parallelogram to represent the atria [10]. It has become increasingly clear that the atria possess a complex three-dimensional structure that is likely highly significant in AF.

6.2.1. Structural factors and reentry

The role of structural factors in reentry is discussed in another paper of the present issue [145], and only a few salient points will be mentioned here. Schuessler et al. first showed that atrial epicardial and endocardial activation can be quite different, presumably due to the role of structural complexities like the pectinate muscles and crista terminalis [146]. In vivo studies have confirmed the importance of the three-dimensional atrial structure in atrial conduction and AF [26]. Pectinate muscles can play an important role in anchoring atrial reentry circuits [147]. The complex fiber arrangement in the region of the pulmonary veins, as well as their role as functional obstacles, may make them privileged sites for intra-atrial reentry, in addition to their well-known tendency to generate ectopic activity.

Atrial structures can also contribute to reentry by virtue of particular ionic and action potential properties. For example, electrical heterogeneity is an important determinant of AF [20] and there are distinct ionic phenotypes in different atrial regions that contribute to baseline action potential and ERP heterogeneity [148,149]. The left atrium is particularly important in AF maintenance [28], partly because larger \( I_{ks} \) in the left atrium results in shorter APDs and ERPs [149]. There is also evidence that pulmonary veins may uniquely manifest ectopic activity and ar-
rhythmogenesis [150–152]. Further delineation of the role of structural factors in AF may be helpful in improving non-pharmacological therapy like ablation procedures.

6.2.2. Privileged sites of ectopic activity—why?

A crucial development in AF pathophysiology was the demonstration of the importance of ectopic activity from specific atrial regions. The mechanistic basis for such activity is still unknown. The picture has recently increased in complexity, with evidence suggesting that AT enhances activity in the regions of the pulmonary veins and ligament of Marshall [153]. This observation raises the question of whether AT-remodeling may promote abnormal impulse formation in addition to favouring reentry.

6.3. Role of the autonomic nervous system

Sympathetic and parasympathetic tone are powerful regulators of electrophysiological function. Vagal stimulation shortens atrial ERP in a spatially heterogeneous fashion [154], with both absolute ERP changes and increased spatial heterogeneity apparently important in AF promotion [18,19,155,156]. Vagal AF has many features of multiple-circuit reentry, and acetylcholine-induced AF was used in a classical demonstration of Moe’s multiple-wavelet hypothesis [157]. The role of multiple-wavelet reentry in vagal AF has been challenged by a number of observations which suggest that vagal AF may be maintained by a local ‘driver’ region, which generates subsidiary wavelets that produce fibrillatory activity without playing a significant role in AF maintenance [28,156,158,159]. In some patients, episodes of AF are clearly triggered by enhanced vagal tone [160], whereas in others vagal tone may play an important permissive role. Patients in whom vagal tone plays an important role may benefit particularly from drugs with vagolytic actions or drugs that inhibit I_{K1}. If there are geographically favoured ‘driver regions’ for vagal AF, local ablation may be effective.

There is evidence for a role of sympathetic tone in some cases of AF, particularly those that are exercise-induced and are associated with organic heart disease [161]. The importance of sympathetic tone is illustrated by the modest but statistically significant ability of pure beta-blockers to prevent AF recurrence after electrical cardioversion [162]. Ablation of the ligament of Marshall may be particularly effective for patients with adrenergic AF [163].

7. Synthesis

7.1. Synthetic view of AF substrates

The information presented above indicates that AF has a potentially complex pathophysiology, with various substrates and mechanisms interacting in a potentially complex fashion. It is therefore important to consider AF substrates in an overall framework rather than in isolation. Fig. 3 illustrates what is known about the ionic determinants of AF. Reentry is governed by the balance between CV and ERP. ERP is controlled largely by APD, with extrinsic and intrinsic determinants as described above. CV can be affected by both AT and CHF-related remodeling. When a substrate for reentry exists, the occurrence of reentry requires a trigger, generally provided by ectopic activity. Reentry could also enhance triggered activity by causing tachycardia-induced Ca^{2+}-loading [61] and thereby enhancing NCX activity. Ectopic activity can result from increased pacemaker current, and decreased I_{K1} may also contribute by bringing the resting potential towards threshold. Extrinsic determinants include upregulation of NCX, I_{K1} downregulation and stretch-related channel activation.

The functional substrates of AF are illustrated in Fig. 4. At the center are the three primary mechanisms postulated in the early 20th century, indicating the continuing importance of these old conceptual frameworks. Recent work has fleshed out many details of the activation of these mechanisms. In addition, we have become aware of the extent to which different mechanisms interact. Ectopic activity and single-circuit reentry can lead to multiple-circuit reentry via AT-remodeling. Either form of reentry can theoretically promote ectopy by causing triggered activity via rate-dependent increases in Ca^{2+}-loading. Furthermore, the clinical context may affect substrate development. For example, CHF leads to a substrate that can maintain AF [102], which will lead to AT-remodeling. However, the electrophysiological effects of AT-remodeling are different in the setting of CHF (less ERP reduction, preserved ERP rate-adaptation) compared to effects in normal hearts [164]. Clearly, should a patient with CHF develop AF, the mechanisms and manifestations will reflect a combination of the initial CHF substrate and AT-remodeling induced changes in the context of the CHF milieu.

7.2. Relevance of AF substrates for new therapeutic approaches

The traditional therapeutic approach to AF was based largely on suppressing reentry by prolonging atrial refractoriness. Advances in understanding AF substrates have led to the identification of new targets for AF therapy (Fig. 5), as well as to appreciating the effects that attacking one target can have on the entire complex of AF mechanisms. Pharmacological targets for reentry include the classical target I_{Ks}, as well as the atrial-specific channel I_{K1} and potentially I_{Ks}. Stretch-operated channels may be a target for both reentrant and ectopic mechanisms, and I_{Na} blockers merit reconsideration, particularly if they can be designed in a fashion that avoids ventricular proarrhythmia. Ectopic activity can be attacked by traditional means like I_{Na} blockade, but Ca^{2+}-loading/DAD related mechanisms are also potential targets as are stretch-related
channels. New pharmacological approaches may directly target either AT- or CHF-related remodeling, with several potentially successful approaches having already been identified. The development of ablation therapy has occurred in parallel with evolving concepts regarding structural AF substrates. Further understanding of these structural motifs will likely lead to improved ablation strategies. Device therapy is still in evolution, but the demonstration that AF often begins as an organized tachycardia [165] has rationalized the use of anti-tachycardia pacemakers and contributed to the usefulness of multimodal therapy devices in AF management. Recognition of the role of atrial conduction abnormalities in the reentrant substrate underlying AF has led to the development of

Substrate-based Therapeutics

<table>
<thead>
<tr>
<th>Ionic targets</th>
<th>Pharmacological</th>
<th>Non-pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reentry</td>
<td>( I_{Kr} )</td>
<td>Ablation</td>
</tr>
<tr>
<td></td>
<td>( I_{Ks} )</td>
<td>Ectopic foci:</td>
</tr>
<tr>
<td></td>
<td>( I_{kur} )</td>
<td>- pulmonary veins</td>
</tr>
<tr>
<td></td>
<td>adrenergic/cholinergic</td>
<td>- ligament of Marshall</td>
</tr>
<tr>
<td></td>
<td>stretch channels</td>
<td>- Venae Cavae</td>
</tr>
<tr>
<td></td>
<td>( I_{Na} )</td>
<td>- coronary sinus</td>
</tr>
<tr>
<td>Ectopic activity:</td>
<td>( NCX/Ca^{2+} ) overload/DADs</td>
<td>(mitral disease)</td>
</tr>
<tr>
<td></td>
<td>( I_{Na} )</td>
<td>Reentry circuits:</td>
</tr>
</tbody>
</table>

Remodeling

<table>
<thead>
<tr>
<th>Atrial tachycardia:</th>
<th>Reentry circuits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( I_{CaT} )</td>
<td>tachycardia/flutter circuits</td>
</tr>
<tr>
<td>( I_{redox} )</td>
<td>single lesions</td>
</tr>
<tr>
<td>other signaling components</td>
<td>for single-circuit reentry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHF:</th>
<th>Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>renin-angiotensin system</td>
<td>Remodeling:</td>
</tr>
<tr>
<td>cell death pathways</td>
<td>atrial cardioverter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MAZE</th>
<th>Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>- tachycardia/flutter circuits</td>
<td></td>
</tr>
<tr>
<td>- single lesions</td>
<td></td>
</tr>
<tr>
<td>- renin-angiotensin system</td>
<td></td>
</tr>
<tr>
<td>- cell death pathways</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Functional AF substrates.

Fig. 5. Substrate-based therapeutic approaches.
atrial pacing approaches, like biaxial pacing, that increase the homogeneity of atrial activation and reduce the risk of AF recurrence [166].

Acknowledgements

The author thanks the Canadian Institutes of Health Research, the Mathematics of Information Technology and Complex Systems (MITACS) Network and the Quebec Heart Foundation for research funding and Luce Bégin for secretarial help with the manuscript.

References

[38] Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with...


[79] Chouabe C, Driči MD, Romey G, Barhanin J, Lazdunski M, HERG
and KvLQT1/IsK, the cardiac K+ channels involved in long QT syndrome, are targets for calcium channel blockers. Mol Pharmacol 1998;54:695–703.


[108] Lie JT, Hammond PI. Pathology of the senescent heart: anatomic syndromes, are targets for calcium channel blockers. Mol Pharmacol 2000;130:669±677.


[115] Lie JT, Hammond PI. Pathology of the senescent heart: anatomic syndromes, are targets for calcium channel blockers. Mol Pharmacol 2000;130:669±677.


