Atrial fibrillation (AF) is characterized by rapid and irregular activation of the atrium, for example, 400–600 pulses of the atrium muscular wall per minute in humans. The occurrence of AF increases with age, with a prevalence rising from 0.5% of people in their 50s to nearly 10% of the octogenarian population. Several cardiac disorders predispose to AF, including coronary artery disease, pericarditis, mitral valve disease, congenital heart disease, congestive heart failure (CHF), thyrotoxic heart disease and hypertension. Many of these are thought to promote AF by increasing atrial pressure and/or by causing atrial dilation; however, the precise mechanistic links are incompletely defined. AF also occurs in individuals without any other evidence of heart or systemic disease — a condition known as ‘lone AF’.

Normally, heart rate is finely attuned to the body’s metabolic needs through physiological control of the cardiac pacemaker function of the sinoatrial node (Fig. 1a), which maintains a rate of about 60 beats per minute at rest and can fire as rapidly as 180–200 times per minute at peak exercise. During AF, atrial cells fire at rates of 400–600 times per minute. If each atrial impulse were conducted to the ventricles, the extremely rapid ventricular rate would lead to ineffective cardiac contraction and rapid death. This is prevented by the filtering function of the atrioventricular (AV) node (Fig. 1b), which has a limited impulse-carrying capacity and through which atrial impulses must pass before activating the ventricles.

The ventricular rate during AF (the effective ‘heart rate’) is thus no longer under physiological control of the sinus node, but instead is determined by interaction between the atrial rate and the filtering function of the AV node. The ventricular rate during AF is typically in the region of 150 pulses per minute in the absence of drug therapy. In normal individuals, a brief period of AF may cause palpitations, chest discomfort and light-headedness. Sustained AF with an uncontrolled ventricular response rate can, by itself, cause severe CHF after several weeks to months, but this is reversible with proper rate and/or rhythm control.

Owing to the loss of effective atrial contraction, and the irregular and excessively rapid ventricular rhythms that can be caused by AF, acute and sometimes life-threatening decompensation of otherwise compensated cardiac disease may occur. The loss of atrial contraction also leads to stasis of blood in the atria, which promotes clot formation and the occurrence of thromboemboli. These thromboemboli tend to propagate, particularly to the brain but also to other organs (including the kidneys, mesenteric circulation and the heart itself), potentially leading to infarction. The thromboembolic risk is reduced by administration of oral anticoagulant drugs, but at the price of an increased risk of bleeding complications. These considerations probably account for the significant role of AF in the occurrence of stroke: AF is the single most important cause of ischaemic stroke in people older than 75 (ref. 4).

Cardiac arrhythmias have been treated traditionally with antiarrhythmic drugs that control the rhythm by altering cardiac electrical properties. However, the available drugs are not specific for atrial electrical activity and can have profound effects on ventricular electrophysiology. For example, K+-channel-blocking drugs that are used to treat AF can mimic potentially lethal congenital disorders of cardiac repolarization, as discussed elsewhere in this issue by Marban, pages 213–218.

It has become apparent over the past 15 years that the effects of antiarrhythmic drugs on the electrophysiology of the ventricles can themselves paradoxically lead to life-threatening rhythm disorders (so-called ‘proarrhythmia’) and increase mortality. There has been, therefore, a shift towards non-pharmacological therapies for cardiac arrhythmias, including controlled destruction of arrhythmia-generating tissue (‘ablation therapy’) and implantable devices that can sense arrhythmias and terminate them with controlled electrical discharges. In contrast to a wide range of other cardiac arrhythmias, for which safe and highly effective non-pharmacological therapies have been developed, AF continues to be a challenge for both pharmacological and non-pharmacological approaches to treatment, which has motivated a search for improved therapeutic modalities. One hope is that a better understanding of the fundamental mechanisms underlying AF will lead to safer and more effective mechanism-based therapeutic approaches.

Here I review the recent evolution of our understanding of the mechanisms of AF, highlighting experimental findings that have produced new insights and questions about the theory of the arrhythmia. In addition, I discuss the potential implications of this knowledge for therapeutic innovation.

Basic mechanisms of arrhythmia

To aid in the comprehension of AF mechanisms, the basic electrophysiological mechanisms of arrhythmia are presented in Fig. 2. Abnormal impulse formation can lead to...
focal ectopic (that is, arising from an area other than the sinus node) arrhythmia generators (Fig. 2a,b). Figure 2a illustrates the mechanism of ‘automaticity’, which is the basis of cardiac pacemaker function. Various areas of the heart can show automaticity, but cardiac rhythmicity is normally controlled by the sinus node, which is intrinsically the fastest pacemaker.

Inward currents (positive ions entering the cell) depolarize the cell membrane (making the cell interior more positive), and outward currents repolarize it (making the cell interior more negative). Pacemaker activity results from a change in the balance of cardiac currents in the resting (diastolic) phase of the action potential, such that inward currents predominate and lead to progressive diastolic depolarization. When the membrane potential reaches a critical value, called the ‘threshold potential’, the cell fires (Fig. 2a, 1). If the slope of diastolic depolarization is increased in a region outside the sinus node (for example, by acute myocardial ischaemia; Fig. 2a, dashed line), the cell will reach threshold earlier and generate ectopic action potentials (Fig. 2a, 2) at a rapid rate.

Abnormal focal activity can also arise from ‘afterdepolarizations’ (Fig. 2b). As discussed in detail elsewhere in this issue (see review by Bers, pages 196–205), the free intracellular Ca²⁺ concentration rises (Fig. 2b). As discussed in detail elsewhere in this issue (see review by Bers, pages 196–205), the free intracellular Ca²⁺ concentration rises sharply during the depolarized (systolic) phase of the action potential, and diastolic relaxation ensues when cytosolic Ca²⁺ is reduced by uptake into the sarcoplasmic reticulum and by extrusion from the cell through transmembrane Na⁺/Ca²⁺ exchange (NCX). The latter process is electrogenic, exchanging three Na⁺ ions for each Ca²⁺ (one net positive charge moves in the direction of Na⁺ transport in each cycle), and produces an inward current during Ca²⁺ extrusion. This inward current can depolarize the cell, generating an afterdepolarization (Fig. 2b, 2). If afterdepolarizations reach the threshold potential (Fig. 2b, 3), spontaneous action potentials will result, producing ectopic firing if they arise in tissues outside the sinus node. This form of afterdepolarization is favoured by conditions that increase NCX current, such as excessive intracellular concentrations of Ca²⁺ and enhanced NCX activity.

Re-entry arises from abnormal impulse propagation between different zones of tissue (Fig. 2c, I and II). After initial depolarization of an action potential, Na⁺ channels are inactivated and the cell cannot be re-fired until the cell repolarizes to a potential (about −60 mV) at which Na⁺ channels recover from inactivation — at time referred to as the ‘refractory period’. An ectopic complex (Fig. 2c, 2) arising in zone II during the refractory period of action potential 1 in zone I will initially fail to activate zone I, but may propagate through an alternative pathway to return to zone I when its refractory period is over, causing reactivation at this site (Fig. 2c, 3). The impulse will now leave zone I and move towards zone II and, if the time to return to zone II is sufficiently long, then zone II will be reactivated (Fig. 2c, 4).

If the conditions are correct (that is, there is an appropriate substrate for re-entry), zones I and II can repeatedly reactivate each other once re-activation has been initiated, resulting in persistent re-entrant activity. Re-entry can occur in a single circuit, producing rapid regular firing, or multiple unstable re-entry circuits can coexist simultaneously, producing more irregular (fibrillatory) activity. The
refractory period is clearly a key determinant of re-entry — long refractory periods make it more likely that the circulating impulse will encounter tissue that is still refractory and will dieout.

**Classical mechanisms of atrial fibrillation**

The conceptual framework for understanding AF mechanisms has been grounded in ideas developed in the early twentieth century. The principal competing notions at the time were that AF is caused by rapidly discharging, spontaneously active, atrial ectopic foci (Fig. 3a), by a single re-entry circuit (Fig. 3b), or by multiple functional re-entrant circuits (Fig. 3c). For multiple-circuit re-entry excitation (Fig. 3c), irregular atrial activity is a consequence of the primary arrhythmia mechanism. For thready focal and single-circuit mechanisms, irregularity is presumed to result from interactions between high-frequency wavefronts produced by the primary generator (the ectopic focus or primary re-entrant circuit) and the spatially variable refractory properties of atrial tissue (fibrillatory conduction).

These mechanisms have significant implications for potential therapies. Multiple-circuit re-entry should be amenable to interventions that interfere with the ability of the re-entering circuits to perpetuate themselves. Such interventions include drugs that increase the refractory period and surgical division of the atria into electrically isolated areas, as exemplified by the 'Maze' procedure.

Ectopic mechanisms would be susceptible to drugs that suppress automaticity and to targeted destruction of ectopic foci by surgery or catheter-based approaches. Single-circuit re-entry should be suppressed by drugs that prolong the refractory period and inhibit re-entry, and by ablating key components of the re-entrant pathway.

Over the past 50 years, multiple-circuit re-entry has been the dominant conceptual model of AF. The ectopic focus and single-circuit concepts fell largely into disfavour. Particularly influential has been the work of Moe and co-workers, who emphasized the role of multiple re-entrant waves in the perpetuation of AF. An important component of this theoretical framework is the concept of the 'wavelength', which was developed by Allessie and colleagues. The wavelength is the distance travelled by the electrical impulse in one refractory period, which is the product of the refractory period and the conduction velocity. If the pathlength of the potential circuit is smaller than the wavelength, the impulse will traverse the circuit and return to its starting point in a time shorter than the refractory period, forcing it to impinge on still-refractory tissue and die out. Thus, the wavelength is the shortest pathlength that can sustain re-entry.

According to the 'leading circle' hypothesis of Allessie et al. (ref. 10; and Fig. 4a), functional re-entry naturally establishes itself in a pathlength the size of the wavelength. The number of re-excitation waves that can be accommodated is then a simple function of atrial size and the wavelength: decreased wavelength decreases the minimum circuit size, which increases the number of circuits that can be accommodated, which in turn favours multiple-circuit re-entry and tends to perpetuate AF (Fig. 4c). Traditionally, therefore, the primary approach to AF has been to increase the refractory period (and thereby the wavelength), which limits the number of functional circuits that can be maintained so that AF cannot sustain itself.

An observation incompatible with leading circle theory is the response of AF to antiarrhythmic drugs that block Na⁺ channels. Such agents are effective in terminating AF, but according to leading circle theory should promote AF because they decrease conduction velocity and thereby decrease the wavelength.

**Observations that challenge the classical viewpoint**

Observations obtained over the past 5 years have challenged the previously prevailing notion that all AF is caused by multiple-circuit re-entry. Optical mapping studies of AF in sheep hearts point to a primary local generator, consisting of either a single small re-entry circuit or an ectopic focus. Left atrial sources of activity seem to be particularly important. Left atrial predominance may be related to the location of the pulmonary veins in the left atrium, which seem to have a highly significant role (ref. 15; and see below), or to ionic differences that lead to shorter left atrial refractory periods that favour re-entry. There is also evidence to show that single-circuit re-entry maintains AF in experimental CHF.

Thus, the recently evolving evidence has thrown us back to the debates of the early twentieth century, suggesting that ectopic activity, single-circuit re-entry and multiple circuit re-entry may all be involved in AF.

**The electrophysiological basis of atrial fibrillation**

Evolving clinical evidence shows that AF almost invariably occurs in a setting of atrial electrical dysfunction that provides a favourable substrate for the arrhythmia. Transmembrane ionic currents are key determinants of the arrhythmia mechanisms shown in Fig. 2. Figure 5a shows a representative human atrial action potential. Inward (depolarizing) currents are indicated by a downward arrow and outward (repolarizing) currents by an upward arrow. Iᵥ is the background current responsible for the considerable resting K⁺ conductance that sets the resting potential to between –70 and –80 mV. Cell firing is caused by rapid depolarization through a large Na⁺ current (I₉Na) that brings the cell from its resting potential to a value in the region of +40 mV, providing the electrical energy for cardiac conduction. The cell then partially repolarizes through a transient outward (repolarizing) currents by an upward arrow.

---

**Figure 3** Conceptual models of atrial fibrillation in the early twentieth century, along with therapeutic implications. Ectopic foci (a) and single re-entrant circuits (b) generating atrial fibrillation can be located in either atrium, but are shown here as arising in the right atrium. In c, atrial fibrillation is maintained by multiple re-entrant circuits with spatial and temporal variability. LA, left atrium; RA, right atrium; RP, refractory period.
outward K⁺ current (I_{Ks}), inactivation of which produces a notch in the action potential. This is followed by a relatively flat portion of the action potential (the 'plateau'), which is maintained by an inward L-type Ca²⁺ current (I_{CaL}). A series of K⁺ currents that activates in a time-dependent way and show little inactivation — the so-called 'delayed rectifiers' (I_{K}) — leads to cellular repolarization. In human atrium, I_{K} has three components: an 'ultra-rapid' component (I_{Kur}), a 'rapid' component (I_{Kr}) and a 'slow' component (I_{Ks}). Spontaneously automatic cells are depolarized by an inward pacemaker current (I_{I}). NCX also carries an inward current during terminal repolarization and for a short time thereafter.

The balance between plateau inward and outward currents determines the action potential duration (APD): increased inward current prolongs the action potential, and increased outward current abbreviates it. APD governs the time from cellular depolarization to recovery of excitability at about ~60 mV; the ionic current balance therefore determines the refractory period and the likelihood of re-entry. Alterations in ionic currents that increase APD and thereby the refractory period can be used to prevent AF. For example, many clinically used drugs prolong APD and refractoriness by inhibiting I_{Kur}. They are effective in preventing AF, but can produce dangerous ventricular arrhythmias by interfering with ventricular repolarization (see review by M. Urban, pages 213–218). I_{Kr} and I_{Ks} are under strong adrenergic control [10], and their stimulation might contribute to AF that occurs in situations of increased adrenergic tone. I_{Kur} is carried by Kv1.5 channels that are expressed functionally in human atrium but not ventricle — inhibiting these channels may provide a means of preventing AF without the risk of ventricular proarrhythmia [11, 12].

An important advance in our understanding of AF was made with the recognition that AF, once initiated, alters atrial electrophysiological properties in a manner that favours the ease of inducing and maintaining the arrhythmia — a process called 'electrical remodelling' [13]. The principal mechanisms involved are shown in Fig. 6. The roughly tenfold atrial rate increase caused by AF is the primary stimulus to remodelling, and similar changes are produced by any form of sufficiently rapid atrial tachycardia [14]. Ca²⁺ enters the cells through I_{CaL} with each action potential, so a tenfold increase in atrial rate substantially increases cellular Ca²⁺ loading [15].

Progressive Ca²⁺ loading threatens cell viability, and the cells respond to minimize the impact of increased rate on intracellular Ca²⁺ load. Short-term defence mechanisms include voltage-dependent and intracellular Ca²⁺-concentration-dependent inactivation of I_{CaL} (ref. 26). Over the longer term, the concentration of messenger RNA encoding the pore-forming α-subunit decreases, which in turn decreases I_{CaL} (refs 30–32). Both short- and long-term decreases in I_{CaL} reduce Ca²⁺ entry and help to prevent Ca²⁺ overload; however, because I_{Kur} is a key contributor to the action potential plateau (Fig. 5), reduced I_{CaL} decreases APD, reduces the refractory period, and promotes the induction and maintenance of AF by multiple-circuit re-entry [16]. AF that begins by any mechanism causes electrical remodelling, which by promoting multiple-circuit re-entry will make this a 'final common pathway' of AF irrespective of the initial mechanism (Fig. 7).

In addition to downregulating I_{CaL}, AF induces many other changes, consistent with a substantial cellular insult caused by excessively rapid activation. Cellular Ca²⁺ handling is altered, decreasing the release of systolic Ca²⁺ (ref. 34) in association with altered concentrations of intracellular Ca²⁺-handling proteins [29, 35]. Cellular myolysis occurs, along with changes that suggest a return to a more fetal phenotype [36]. Decreased release of systolic Ca²⁺ and myolysis impair atrial contractility, contributing to the occurrence of atrial blood stasis and thromboembolic events after termination of AF [37]. I_{Kur} seems to be decreased, possibly contributing to a slowly developing decrease in atrial conduction that may help to promote AF [38, 39]. I_{Kr} is decreased [30, 32, 39], and I_{Ks} may be altered [29, 39]; however, the physiological significance of these changes in K⁺ current are currently unclear. Finally, AF has been associated with altered expression of connexin channel proteins that govern intercellular electrical communication [40–42]. There is evidence for spatially heterogeneous reductions in expression of connexin 40 (ref. 41), but the results of available studies have been inconsistent [40–42] and the significance of these changes in connexin remains unclear.

Experimental CHF also promotes AF and produces atrial ionic remodelling [43]. In CHF, inward I_{CaL} is reduced much less (~30%) than in atrial tachycardia remodelling (~65%). Outward I_{Kur}, which is unaffected by atrial tachycardia, is decreased by about 30% and inward NCX is increased [44]. Thus, unlike atrial-tachycardia-induced ionic remodelling, CHF-induced remodelling does not reduce APD and does not in itself favour re-entry. By contrast, CHF changes the architecture of atrial tissue, causing a substantial increase in fibrous tissue content (fibrosis) within and between muscle bundles, which interferes with electrical conduction and causes AF that often seems to be due to single-circuit re-entry [17, 18, 44]. In addition, the increased NCX promotes afterdepolarization-related atrial ectopic firing and AF [45]. Figure 5 summarizes the ionic determinants of AF, including both intrinsic and extrinsic determinants.

Molecular and genetic factors in atrial fibrillation

Although electrical remodelling accounts for the self-promoting nature of AF once it has begun, other factors must lead to the initial occurrence of AF. Individuals affected with AF are known to have upregulated levels of atrial extracellular signal-related kinase (ERK) and angiotensin-converting enzyme (ACE) [46], but a decreased density of angiotensin-II type 1 receptors and an increased density of angiotensin-II type 2 receptors [47]. Carboxypeptidase activity and

---

**Figure 4** Models of re-entry and implications for atrial fibrillation. **a**, Mechanism of functional re-entry in the leading circle model [10], b, Spiral wave model of re-entry. c, Role of wavelength in the stability of atrial fibrillation according to the leading circle model. The size of functional re-entry circuits depends on the wavelength. Short wavelengths allow several simultaneous circuits to be maintained, favouring continuation of atrial fibrillation. Drugs that increase the wavelength reduce the number of circuits that can be accommodated, favouring termination of atrial fibrillation. CV, conduction velocity; PL, path length; RP, refractory period; WL, wavelength.
activated protein kinases including ERK. A rise in atrial caspase-3 concentrations of angiotensin-II and by activation of mitogen-experimental CHF, the promotion of AF is preceded by increased enzyme caspase-3, which suggests that apoptosis is occurring. In AF-affected individuals shows both nuclei that are positive for nick end labelling and increased concentrations of the apoptotic TUNEL (terminal deoxyribonucleotide transferase-mediated dUTP nick end labelling) and increased concentrations of the Ca2+ current has been difficult to demonstrate in human atrial tissue. Conduction properties are determined by the function of Na+ channels and connexins. Reductions in outward currents increase the refractory period, prevent atrial fibrillation. Increased inward current and increases in Na+/Ca2+ exchange promotes afterdepolarization-related ectopic activity, which can trigger re-entry in the presence of an appropriate substrate or cause atrial tachycardias that induce electrical remodelling and produce a re-entry substrate. Activation of stretch-induced channels can promote both ectopic activity and re-entry. Inhibition of ACE reduces CHF-induced activation of ERK and fibrosis, and also decreases the AF-promoting effects of CHF. The effectiveness of ACE inhibition shows that interrupting signalling pathways can prevent development of the AF substrate — a process that might potentially be used in new therapeutic approaches. A recent study supporting this notion showed that ACE inhibition reduces the incidence of AF after myocardial infarction in people with left ventricular dysfunction.

Atrial fibrillation can occur on a familial basis, pointing to a genetic cause of the arrhythmia in some individuals. Linkage analyses have identified possible loci on chromosome 10 in two kindreds. Identifying the gene of susceptibility, coupled with defining the sequence and function of the protein that it encodes, hasthe potential to provide both insight into the pathophysiology of the arrhythmia and diagnostic tools with which to identify susceptible individuals. Studies of transgenic mouse models of AF are still in their infancy but promise to advance our understanding of the role of defined genes in the pathophysiology of the arrhythmia. Mice with a homozygous deficiency in the gene encoding connexin 40 have slowed intra-atrial and AV nodal conduction, along with inducible atrial tachyarrhythmias. Mice overexpressing cardiac RhoA, a low molecular-weight GTPase, develop atrial fibrillation and AV block, and show progressive deterioration of ventricular function. Mice with cardiac overexpression of a constitutively activated form of transforming growth factor-β have atrial but not ventricular fibrosis. In addition, preliminary data suggest that these mice are susceptible to AF, compatible with the notion that atrial fibrosis is an important AF-promoting factor.

The molecular events leading to ionic remodelling remain incompletely understood. On the basis of evidence indicating that Ca2+ overload has a central role in AF, the efficacy of I\textsubscript{Na}, blockers in atrial tachycardia remodelling has been studied. L-type Ca2+-channel blockers are effective in short-term remodelling, but are ineffective in remodelling caused by longer periods of atrial tachycardia. Mibefradil, a drug that blocks both L-type Ca2+ channels and the high-threshold T-type Ca2+ channels, prevents atrial tachycardia remodelling effectively, but it remains uncertain whether this action is due to inhibition of I\textsubscript{Na} or to collateral drug actions. The T-type Ca2+ current has been difficult to demonstrate in human atrial myocytes. Recent work has suggested that oxidant stress may be
involved in atrial tachycardia remodelling, and that ascorbic acid may be beneficial in preventing AF that occurs after cardiac surgery.

Theories supporting a pulmonary vein origin

Another important advance in our understanding of the pathophysiology of AF has been the demonstration by Haissaguerre et al. of the importance of pulmonary vein foci in initiating arrhythmia. AF may begin as a rapid atrial tachycardia from the pulmonary veins, with tachycardia remodelling promoting the transition to multiple-circuit re-entry. Ectopic foci from other sources, such as the ligament of Marshall (a venous remnant in the left atrium) and the superior vena cava, may also be important in initiating AF, although pulmonary veins remain the most common source of focal activity. More recently, rapid pulmonary vein activity has been shown to be promoted by atrial tachycardia remodelling, and to have a role in maintaining (and not just initiating) AF.

The underlying basis of pulmonary vein activity remains poorly understood. In 1981, Cheung showed that cardiac tissue in the sleeves around the proximal ends of pulmonary veins can generate action potentials and shows slow spontaneous activity. The rate of pulmonary vein activity can be greatly accelerated by adrenergic stimulation. It is not yet clear whether the pulmonary veins have a role that is limited to action potential generation, or whether (owing to the geometric arrangement of cardiac fibres around the veins or because of strands of poorly coupled cardiac tissue overlying vascular smooth muscle) they provide preferential zones for re-entry.

The pulmonary veins are subjected to stretch from pulsatile blood flow. The stretch-induced non-selective cation current ($I_{\text{ns}}$) can carry Na$^+$ into the cell or K$^+$ out. It depolarizes the cell at the resting potential (favouring ectopic activity) and repolarizes it during the depolarized phase positive to 0 mV, decreasing APD and promoting re-entry. $I_{\text{ns}}$ may have a role in AF initiation in the pulmonary veins or other atrial tissues subjected to stretch. A tarantula toxin that specifically inhibits $I_{\text{ns}}$ suppresses AF related to acute stretch in rabbit hearts. The toxin may prove useful as an experimental tool, as well as a lead for antiarrhythmic agents that specifically antagonize stretch-related electrophysiological perturbations.

The sinoatrial node and atrial fibrillation

There is a clinical association between abnormalities of sinoatrial (SA) node function and AF. At one time, this observation and the characteristic slow conduction within the sinus node led investigators to speculate that the sinus node might be involved in maintaining the arrhythmia. The data available at present suggest that the sinus node is probably passive during AF, with atrial impulses invading the SA node at a rate much faster than its intrinsic frequency. The association between sinus node dysfunction and AF is probably due to diseases that affect both the SA node and atria simultaneously, rather than participation of SA node pathology per se in AF.

Recent work has provided exciting insights into the molecular basis of the pacemaker current $I_N$. A family of cyclic-nucleotide-binding subunits, called the HCN family, underlies $I_N$, function in the sinus node and other cardiac regions. Further work on HCN channels may provide interesting insights into the molecular basis of
normal and abnormal cardiac pacemaker function, and may provide important knowledge regarding the pathophysiology of AF and other cardiac arrhythmias.

Theoretical aspects

The development of ‘spherical wave’ theory has provided a new model for the fundamental properties of cardiac re-entrainment (ref. 77; and Fig. 4b). According to this theory, re-entrainment is maintained through the ability of spiralling waves to perpetuate in media with sufficient excitability to support the angle of spiral curvature. Evidence has been provided for a non-activated, excitable core at the centre of re-entrainment circuits in AF—by spiral wave re-entrainment in the isopotential loops (88)—that is consistent with spiral wave re-entrainment in the isopotential loops. This theoretical work can account for recent experimental observations of the action of class I antiarrhythmic drugs in AF.

Synthesis and future directions

The sole, multiple-circuit re-entrainment mechanism for AF, which was the predominant notion for about 50 years until the mid-1990s, has been challenged by more recent work showing the complexity of AF mechanisms and the validity of competing concepts proposed in the early twentieth century. Furthermore, the inter-relationships among AF mechanisms and the determinants of their occurrence have been highlighted (Fig. 7), raising several new questions. What are the molecular signals leading from atrial tachycardia to electrical remodelling? By what signalling mechanisms does CHF lead to atrial fibrosis and atrial ionic remodelling? What are the mechanisms of AF associated with hypertension, coronary artery disease, thyrotoxicosis and senescence? Why do the pulmonary veins seem so important in initiating, and possibly maintaining, AF? How do atrial tachycardia affect pulmonary vein activity? What are the precise, relative roles of atrial tachycardia, single-circuit re-entrainment and multiple-circuit re-entrainment in maintaining clinical AF? What are the genes responsible for familial AF, and how do they lead to the arrhythmia? Can improved knowledge of the dynamical basis of AF lead to pacing modalities that can prevent or stop the arrhythmia? Can interventions against remodelling safely and effectively prevent the development of the substrate for AF?

In the near future, the answers to these and related questions are likely to increase our understanding of the mechanisms underlying AF and to lead to new and improved possibilities in prevention and therapy.

---

15. Allessie, M. A., Bonke, F. L. & Schopman, F. J. C. Leading circle theory (Fig. 2a). According to this theory, re-entrainment is maintained through the ability of spiralling waves to perpetuate in media with sufficient excitability to support the angle of spiral curvature. Evidence has been provided for a non-activated, excitable core at the centre of re-entrainment circuits during AF—by spiral wave re-entrainment in the isopotential loops (88)—that is consistent with spiral wave re-entrainment in the isopotential loops. This theoretical work can account for recent experimental observations of the action of class I antiarrhythmic drugs in AF.
insight review articles


