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BASIC MECHANISMS OF ATRIAL FIBRILLATION—VERY NEW INSIGHTS INTO VERY OLD IDEAS

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■ **Abstract** Atrial fibrillation (AF) was recognized and studied extensively in the early twentieth century, but many fundamental aspects of the arrhythmia were poorly understood until quite recently. It is now recognized that AF can be initiated by a variety of mechanisms that share the ability to cause extremely rapid, irregular atrial electrical activity. Once initiated, AF causes alterations in atrial electrical properties (electrical remodeling), including both rapid functional changes and slower alterations in ion channel gene expression, which promote the maintenance of AF and facilitate reinitiation of the arrhythmia should it terminate. Electrical remodeling decreases the atrial refractory period in a heterogeneous way, thus decreasing the size and stability of potential functional atrial reentry waves and promoting multiple-circuit reentry. Whatever the initial cause of AF, electrical remodeling is likely to be a final common pathway that ultimately supervenes. Recent advances in understanding ion channel function, regulation, and remodeling at the molecular level have allowed for a much more detailed appreciation of the basic determinants of AF. Improvements in the clinical management of AF will inevitably follow the recent advances in our understanding of its detailed pathophysiology.

INTRODUCTION

Atrial fibrillation (AF) is currently the most common sustained clinical arrhythmia and is responsible for a substantial proportion of hospital costs incurred in the treatment of cardiac rhythm disorders (1). AF becomes increasingly common with age, having an incidence averaging $<0.5\%$ in patients <40 years of age and reaching a prevalence of $>5\%$ in patients >65 (2). Thus, AF is likely to become increasingly important with the aging of the population. The arrhythmia is defined by a very rapid atrial rate (generally >400/min in humans) along with irregular

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atrial activation and a lack of a repetitive pattern of coordinated atrial activity on the electrocardiogram (ECG). AF is associated with a variety of complications, including thromboemboli resulting from coagulation in the relatively static atrial blood pool, a loss of the fine adjustment of ventricular rate to the body's precise metabolic needs, potential impairment of cardiac function (particularly if the ventricular response is rapid), and subjective symptoms like palpitations, dizziness, breathlessness, and chest pain.

HISTORICAL OVERVIEW

Early Ideas About Atrial Fibrillation Mechanisms

In the latter half of the nineteenth century, Vulpian first described the induction of ventricular and atrial fibrillation by electrical shocks (3). At the turn of the century, Cushny suggested that AF might be the cause of highly disorganized rhythms (delirium cordis) in man (4). Fredericq demonstrated this experimentally by cutting the bundle of His and thereby regularizing the ventricular rhythm in the presence of AF (5). In 1913, Mines suggested that fibrillation was a type of reentrant process, requiring that the length of the excitation wave be shorter than the column of muscle on which it occurred (6). Both Mines (7) and Garrey (8) presented concepts of fibrillation as maintained by multiple-simultaneous-reentrant circuits. Garrey published a detailed review of the state of knowledge regarding AF in 1924 (9). Although he presented a consensus supporting the multiple-functional-reentry-circuit concept of AF, he pointed out alternative views of AF as caused by atrial hyperexcitability (one or more rapidly discharging atrial ectopic foci) or to a single, dominant mother wave with fibrillatory conduction. These notions of mechanisms underlying AF are portrayed schematically in Figure 1.

The Multiple Wavelet Hypothesis

In 1959, Moe & Abildskov (10) showed that AF could be produced by experimental paradigms of both multiple circuit reentry and rapid activity, and they suggested that either type of mechanism might cause clinical AF. Gordon Moe put forward the "multiple wavelet hypothesis" of AF in 1962 (11). This concept differed from previous multiple-circuit-reentry notions in that, rather than thinking of reentry waves that return to some initial starting point, Moe described propagation during AF as involving multiple independent wavelets circulating around functionally refractory tissue. In this concept, the trajectory of some wavelets leads them into paths of reduced excitability, causing them to extinguish, whereas other wavelets are able to propagate through tissues of adequate excitability and maintain themselves and/or spawn daughter wavelets. The maintenance of AF then depends on the probability that electrical activity can be

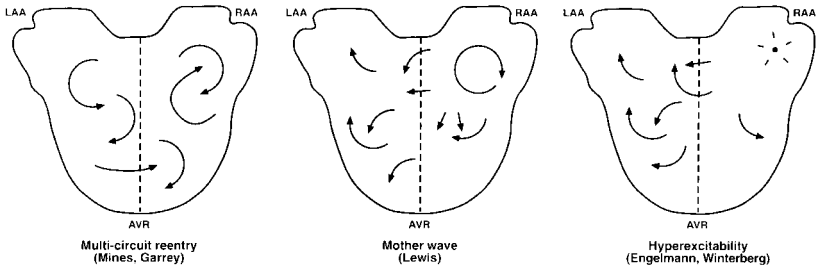

Figure 1 Schematic representations of concepts of atrial-fibrillation mechanisms held by various investigators in the early twentieth century. The atria are represented in an unfolded manner, with a dashed line indicating the position of the septum. Mines & Garrey believed that AF is caused by multiple, simultaneous functional reentry circuits. Lewis held that AF is maintained by a single, rapid atrial reentry circuit with variable conduction through atrial tissue (because some regions are unable to follow the very rapid primary frequency), producing rapid, irregular activation. Engelmann & Winterberg supported the notion that rapidly discharging ectopic foci maintain the arrhythmia. LAA, left atrial appendage; RAA, right atrial appendage; AVR, atrioventricular ring.

sustained by a sufficient number of active wavelets at any time. This idea is best understood as a more quantitative refinement of earlier ideas than as a truly novel conceptualization. The implications of the multiple-wavelet hypothesis were evaluated in 1964 with a simple two-dimensional cellular automaton-based computer model (12). Experimental support for Moe's ideas was obtained subsequently with the use of computerized mapping of AF maintained in the presence of acetylcholine in dog hearts (13).

Important Recent Developments

Two types of recent developments have had particularly important consequences for our understanding of AF mechanisms. The first was the demonstration in 1995 that AF itself alters atrial electrophysiology in ways that promote the occurrence and maintenance of AF (14). Subsequent work on this process of atrial remodeling has provided important insights into a wide range of mechanisms involved in AF at the organ, cell, and molecular levels. The second development was the emergence of evidence for rapidly discharging atrial foci in some clinical forms of AF (15) and for a mother wave form of mechanism in experimental AF (16, 17). These observations reflect back to ideas prevalent in the early twentieth century, as outlined above, and suggest that each of the competing theories of AF may accurately describe the mechanism of AF in particular circumstances. In addition, they point to a dynamic and potentially multifaceted perspective on the arrhythmia, as further discussed below.

Conceptual Models of Reentry and Relationship to Atrial Fibrillation

Closed-Circuit Reentry Multiple-circuit reentry clearly plays an important role in AF. The precise mechanisms involved in multiple-circuit reentry and the underlying determinants have been the subject of considerable development. Mines considered that reentry occurs in "closed circuits in the myocardium" (6). The determinants of this form of closed-circuit reentry are illustrated in Figure 2 (left). The inexcitability of the core that underlies the substrate may be caused by the anatomical arrangement of potential conducting pathways, by anatomical obstacles like the venae cavae or pulmonary veins, or by a region of inexcitability caused by heart disease. Because the size of the circuit is fixed, reentry depends critically on a circuit time that is greater than the refractory period, and the circuit time equals the path length divided by conduction velocity. The refractory period determines whether reentry can be maintained (for reentry to occur, the refractory period must be less than circuit time), but does not directly affect circuit time or tachycardia rate.

Leading-Circle Reentry A great limitation of the closed-circuit reentry concept is that it does not account for the dynamic nature of reentry in arrhythmias like AF, in which the reentry substrate appears functional rather than fixed, as pointed out by Garrey in 1924 (9). Allessie et al presented the first detailed conceptual model of functional reentry in 1977 (18). Reentry is maintained in a leading circle, which establishes itself in the smallest circuit that can maintain continuous activity

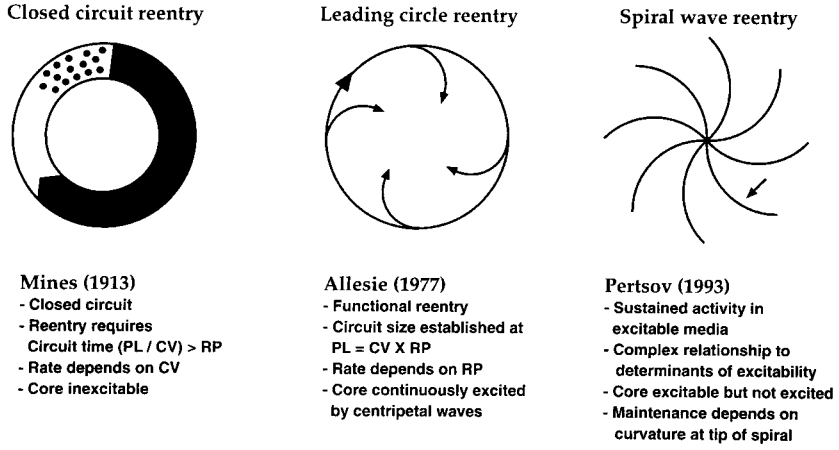

Figure 2 Schematic diagrams of closed-circuit reentry (*left*), leading-circle reentry (*middle*), and spiral-wave reentry (*right*). PL, path length; CV, conduction velocity; RP, refractory period.

(Figure 2, *middle*). This minimum circuit size for reentry is given by the wavelength, a concept first presented by Mines (6) and later quantified by Wiener & Rosenblueth (19) as the product of conduction velocity and refractory period. The core of the reentry circuit is continuously invaded by centripetal impulses from the circulating reentrant wave and is thus continuously excited. A change in conduction velocity causes the reentrant impulse to move concentrically based on the path length traveled in one refractory period; increased conduction velocity moves the wave outwards, to travel in a larger orbit, whereas decreased conduction velocity allows the wave to move inwards to a smaller path. Because the circuit time equals the refractory period (by definition in a path equal to the wavelength), refractory period is the sole determinant of circuit time and tachycardia rate.

Spiral-Wave Reentry More recently, Pertsov et al suggested that the concept of spiral wave activity, a generalized form of continuous activity in excitable media, may be applicable to cardiac reentry (20). As indicated in Figure 2 (right), spiral-wave reentry differs from the other models in that the core is fully excitable. Maintenance of spiral-wave reentry depends on the curvature of wavefronts at the tip of the spiral (21). A present limitation on the applicability of the spiral-wave concept is the difficulty of formulating predictions regarding the stability and rate of reentry based on simple electrophysiological properties like conduction velocity and refractory period.

Experimental Evidence The experimental observations available in support of specific models of reentry are limited. The leading-circle concept suggests that the number of waves that the atria can accommodate should be related to the wavelength, which should give the size of functional reentry circuits. Rensma et al (22) noted that the ability to induce AF in dogs is related to the wavelength under various conditions, with wavelengths under $\sim$7.5 cm associated with AF. Antiarrhythmic drugs that increase the wavelength at rapid atrial rates terminate vagotonic AF by reducing the number of functional circuits to the point that AF fails to sustain itself (23–25). The rate of functional reentry during AF (as indicated by the AF cycle length) appears related to the refractory period, rather than the wavelength, which is consistent with the predictions of the leading-circle model (26). On the other hand, high-density mapping data have been presented that provide direct evidence for the presence of spiral waves with an excitable core during atrial reentry (27). To complicate matters further, anatomical obstacles (28) and structures like pectinate muscles (29) can serve to stabilize and anchor spiral waves. It is questionable whether any form of stable reentry, as implied by the simplest interpretation of the models illustrated in Figure 2, can account for all of the complex activity associated with AF. Indeed, high-density optical mapping during AF in sheep hearts failed to show any complete reentry circuits (30). In this regard, Moe's notion of the maintenance of AF being a probabilistic function of the number of meandering wavelets that are able to propagate successfully

(11, 12) is appealing. Alternatively, Jalife et al (31) have argued that AF may be maintained by a dominant rotor, somewhat akin to Lewis's mother wave concept. In such a case, the failure to detect discrete reentry may simply be due to inadequate resolution of recording techniques in the region of the dominant reentry circuit.

ELECTROPHYSIOLOGICAL DETERMINANTS OF ATRIAL FIBRILLATION: IN VIVO OBSERVATIONS

Effects of the Autonomic Nervous System on Atrial Fibrillation Induction and Maintenance

Cholinergic mechanisms have long been know to play an important role in the occurrence and maintenance of AF. In 1914, Rothberger & Winterberg showed that vagal stimulation converted atrial flutter into fibrillation (32), and Garrey (9) cited the work of numerous investigators who established in the early twentieth century the AF-promoting role of vagal-nerve activation (9). Vagal stimulation or acetylcholine administration has been used in many studies evaluating basic mechanisms of AF and/or its response to antiarrhythmic drug therapy (13, 18, 24–26, 33). Vagal-nerve stimulation decreases the atrial refractory period in a spatially heterogeneous way (34, 35). The vagally mediated decrease in refractory period reduces the wavelength and the size of potential reentry circuits, resulting in multiple-circuit reentry (13, 24–26), although at least one study has suggested that, at very high acetylcholine concentrations, AF may be maintained in isolated canine right atrial preparations by a single rapid microreentry circuit (36). Increases in refractoriness heterogeneity appear to be particularly important in the AF-promoting effects of vagal stimulation (37, 38). The atrial repolarization heterogeneity-promoting effects of vagal stimulation may be caused by patchy distribution of vagal nerve terminals and acetylcholine receptors; however, unmasking of underlying cellular action potential heterogeneity by reducing the space constant may also play an important role (39). Vagal nerve stimulation increases the duration of induced AF, with moderate vagal stimulation often permitting AF to be sustained indefinitely. In addition, vagal stimulation greatly promotes the initiation of AF by single premature atrial activations. This action appears to depend both on refractoriness shortening at the site of premature impulse generation and on heterogeneous effects that cause the premature wave front to block in a region with a lesser degree of refractoriness abbreviation (37).

Role of the Sympathetic Nervous System

Whereas the role of vagal-nerve activation in promoting experimental (9, 24–26, 38) and clinical (40, 41) AF is clear, the role of sympathetic activation is much more murky (38, 40, 41). Sympathetic-nerve stimulation abbreviates atrial refrac-

toriness, but, for a comparable degree of refractoriness and wavelength abbreviation, bilateral sympathetic outflow stimulation has a much smaller AF-promoting action than bilateral cervical vagal-nerve stimulation (38). This difference may be caused by a much more spatially heterogeneous effect of vagal stimulation. Nonetheless, sympathetic activation may be important in some types of AF, particularly in the early phases after cardiac surgery (42). There is evidence that patients with larger atrial L-type Ca^{2+} current ($I_{Ca.L}$) may be more prone to postoperative AF (43), suggesting a role for mechanisms (like arrhythmogenic afterdepolarizations) favored by cellular Ca^{2+} overload. If so, the role of sympathetic activation in postoperative AF might be explained by the I_{Ca}-enhancing effects of β-adrenoceptor stimulation.

Animal Models of Atrial Fibrillation Involving Atrial Dilation and/or Inflammation

Congestive heart failure (CHF) is the single strongest clinical predictor of AF, with even asymptomatic left-ventricular dysfunction significantly increasing the risk of the arrhythmia (44). Boyden et al (45, 46) studied the cellular electrophysiological properties of atrial preparations in animals with spontaneous atrial tachyarrhythmias, including AF, occurring in association with atrial dilatation caused by chronic mitral-valve disease (45) or cardiomyopathy (46). Action potential abnormalities were subtle, consisting of reduced resting potential, decreased phase-0 upstroke velocity, and increased action potential duration (APD) in the most affected cells (46). A striking finding was marked structural derangement, with large amounts of interstitial fibrosis and cellular hypertrophy (45, 46).

Experimentally induced chronic CHF promotes AF, the occurrence of which is related to plasma norepinephrine concentrations (47). Recent work suggests that CHF produces a substrate for AF by causing marked interstitial fibrosis, which results in localized conduction abnormalities and promotes macroreentry, which in many cases resembles mother-wave reentry (16, 48). Figure 3 shows an epicardial activation map during AF in one dog with experimental CHF. Note the presence of an apparent, relatively stable reentry circuit involving the right atrium, Bachmann's Bundle, and the septum. Although AF was clearly present on the surface ECG and electrogram activity was quite irregular in rate and morphology in some regions, electrograms from the zone of the apparent reentry circuit showed substantial regularity (Figure 3*A*). Furthermore, the overall activation pattern was basically similar over three consecutive cycles (Figure 3*B–D*), 10 cycles earlier (Figure 3*E*) or 10 cycles later (Figure 3*F*). These findings are consistent with mother-wave reentry as illustrated schematically in Figure 1 (*middle*).

The ability of interstitial fibrosis to interfere with anisotropic atrial conduction and promote atrial reentry is well documented (49). Interstitial fibrosis is commonly seen in clinical conditions associated with AF such as mitral valve disease,

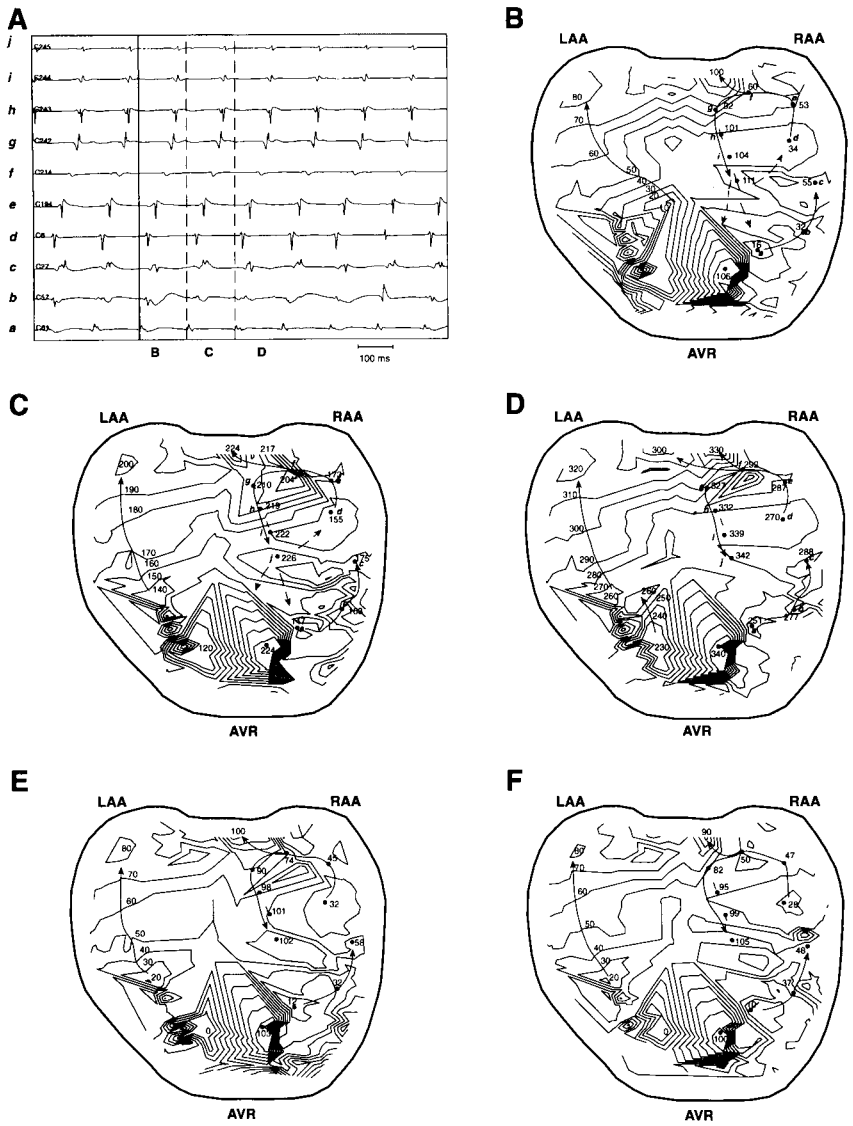

Figure 3 Example of electrograms (*A*) and activation maps (*B-F*) during sustained atrial fibrillation in a dog with CHF. Computerized mapping was used to create activation maps with the use of 243 bipolar electrodes covering the atrial epicardial surface. Five bipolar electrograms were also recorded form the septum. The lines on the activation maps are 10-s isochrones. The locations of electrodes *a* through *j* (of panel *A*), for which electrograms are shown, are indicated in panels *B-D.* Panels *B–D* are activation maps of consecutive cycles corresponding to the time frames indicated in *A.* Panel *E* is a map of a cycle 10 cycles before the window illustrated in *A,* and panel *F* shows activation 10 cycles after the window in *A.* Note the relative regularity of electrograms within the putative reentry circuit and the consistency of the overall activation pattern in *B-F.* Electrode sites *g* through *j* were in the septum, and their activation times were not used in isochrone construction (because they were out of the plane of the other electrode sites).

CHF, and senescence (50–53). Furthermore, interstitial fibrosis is also a common finding in patients with lone AF, unassociated with clinically evident heart disease (54). Thus, the substrate for AF in dogs with experimentally induced heart failure (16, 48) may also apply to many clinical forms of the arrhythmia.

Another animal model that has been used to study AF is sterile pericarditis in the dog (55, 56). AF in this model is caused by a limited number of unstable reentry circuits (55), which appear to involve the interatrial septum preferentially. More recently, evidence for mother-wave reentry has been obtained in the model (17). The precise electrophysiological alterations responsible for AF in association with sterile pericarditis are unclear, but a combination of subtle conduction changes and anatomically based factors may be involved (55, 56).

Atrial Remodeling Induced by Atrial Fibrillation and Atrial Tachycardia

A particularly important recent development in our understanding of the mechanisms of AF was the demonstration that AF alters the atrial electrophysiological milieu in a way that promotes its own maintenance. Wijffels et al (14) very elegantly demonstrated that, when AF is maintained in goats by electrical-burst stimulation whenever sinus rhythm supervenes, the interval between spontaneous reversions increases progressively from several seconds to hours or even days when AF is maintained for up to 2 weeks (Figure 4). Wijffels et al have very descriptively coined this phenomenon "AF begets AF." The AF-promoting effect

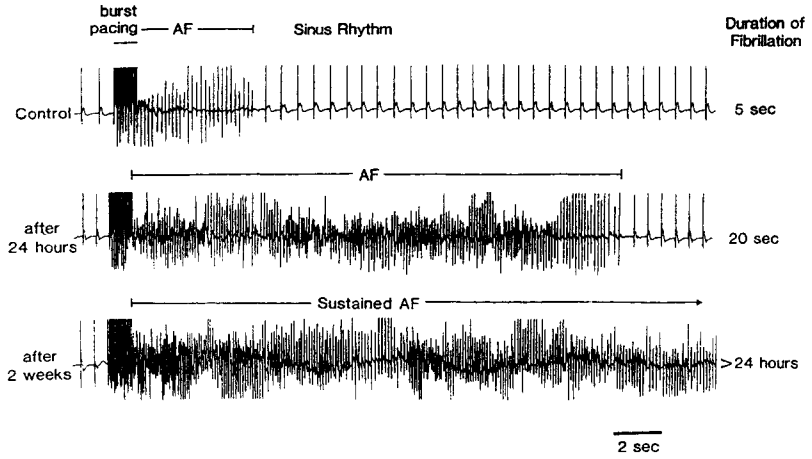

Figure 4 Duration of atrial fibrillation induced by electrical-burst pacing in a chronically instrumented goat after atrial fibrillation had been maintained for the durations indicated to the left of each panel (reproduced from reference 14, by Wijffels et al, with the permission of the American Heart Association, Inc).

of AF is associated with a progressive decrease in atrial effective refractory period (ERP) and in the AF cycle length, an indicator of ERP during AF. Similar changes are observed after either electrically maintained AF (14, 57) or atrial pacing at rates of ≥400 beats per minute (bpm) (58–60). Wijffels et al evaluated several potential mediators of the changes produced by AF and found that atrial tachycardia alone appears to be the primary factor, with no detectable contribution from I_{KATP} activation, changes in autonomic tone, atrial stretch, or atrial natriuretic peptide release (61). Atrial tachycardia causes atrial ultrastructural changes, including mitochondrial swelling, mild cellular hypertrophy, sarcoplasmic-reticulum degeneration, loss of myofibrils, and glycogen accumulation (58, 59, 62). Changes in intercellular junction proteins may occur, but the published findings are somewhat inconsistent, with one study showing that AF increases connexin43 expression (63) and another suggesting that connexin43 is unaltered, but connexin40 is decreased in a patchy fashion (64).

Recovery from the changes induced by 2 to 8 weeks of atrial tachycardia occurs within 24 to 48 h (14, 65). Tachycardia-induced changes in left atrial refractoriness may recover somewhat more slowly compared with ERP changes in Bachmann's Bundle or the right atrium, producing a transient exaggeration in atrial refractoriness heterogeneity (65). Progressive increases in atrial ERP and ERP rate adaptation have been observed within several days after cardioversion of longstanding AF in humans (mean duration >5 years), indicating substantial reversibility of remodeling-induced changes after even very long periods of atrial tachycardia (66).

In addition to decreasing atrial ERP, long-term atrial tachycardia appears to slow intra-atrial conduction (57, 58, 60), thus tending to decrease the wavelength for reentry. Furthermore, changes induced by remodeling are spatially heterogeneous, increasing the heterogeneity in atrial refractory properties (67). The combination of decreased wavelength and increased heterogeneity would be expected to promote multiple-circuit reentry. Epicardial mapping studies have provided evidence for a progressive increase in the number of apparent reentry waves during AF as atrial tachycardia-induced remodeling develops (60), consistent with increased stability of multiple-circuit reentry underlying AF promotion by atrial tachycardia.

Tachycardia-Induced Remodeling and Multiple-Circuit Reentry as a Final Common Pathway for Atrial Fibrillation

The evolving information regarding atrial tachycardia-induced remodeling has fundamental implications regarding the mechanisms of AF. Since all cases of AF involve very rapid atrial activation, tachycardia-induced remodeling will inevitably follow, irrespective of the mechanisms initially involved. Thus, even if AF begins as a result of other mechanisms, such as single reentrant circuits (mother waves) with fibrillatory conduction or rapid ectopic activity, tachycardia remod-

eling will act as a final common pathway to reduce the wavelength in a heterogeneous fashion and promote multiple-circuit reentry.

In Vivo Observations Regarding Atrial Fibrillation Mechanisms in Humans

Clinical studies point to an important role in AF for electrophysiological properties that form a substrate for reentry. Patients with AF tend to have shorter atrial refractory periods (68, 69) and greater dispersion in atrial refractoriness (68, 70, 71) and atrial repolarization times (72). The regional dispersion in atrial repolarization times increases with aging (73), consistent with the known age-related increase in AF prevalence. In addition, atrial conduction abnormalities are observed in patients with AF (69, 74, 75) and are exaggerated in response to atrial premature stimulation (75).

AF is frequently initiated by atrial premature beats (76, 77). Consistent with experimental observations (37, 67), sites at which AF can be initiated are characterized by shorter refractoriness compared with sites at which premature beats do not initiate AF (68). Variable trends in heart rate and ectopic activity have been observed before the onset of AF (77–79). Circadian periodicity has been noted (80) in the duration of AF episodes and the time of AF termination, both pointing to a minimum probability of AF maintenance around midday (11 AM). These observations suggest a role of autonomic and/or neurohumoral factors in AF maintenance, one possible candidate being vagal tone, which tends to be greatest at night and least at midday.

Activation mapping in patients points to different forms of atrial activation during AF (81, 82), which have been divided into three subtypes of AF based on the complexity of activation (81). Individual patients tend to have a predominance of activation subtypes, although individual activation sequences in any patient may fall into any subtype (81, 83). The mechanistic significance of AF subtyping is at present unknown. Local capture of atrial tissue is possible during AF (84), paralleling previous animal studies (85) and consistent with the presence of excitable gaps or regions outside the primary reentry circuit during AF. Signal processing points to a spatial organization of clinical AF (86, 87). Mapping during AF in some patients points to the presence of dominant macroreentry circuits (88, 89), consistent with the observations in dogs with CHF-related AF (16) as illustrated in Figure 3. Other studies point to the role of rapidly firing ectopic foci in patients with AF that tend to be younger and to have very frequent atrial ectopic activity (15, 90).

Clinical Manifestations of Atrial Fibrillation-Related Remodeling

Although the concept of AF-induced remodeling was first established by Wijffels et al in 1995 (14), earlier clinical observations are in agreement with the expected consequences of tachycardia-related atrial remodeling. Since the 1920s, it has

been recognized that the greater the duration of persistent AF, the more resistant AF is to therapy (91), consistent with changes in the AF substrate caused by the arrhythmia itself. Attuel et al (92) noted, in 1982, that patients with high vulnerability to AF had a blunted response of atrial refractoriness to heart rate, consistent with changes typical of remodeling (14, 57, 60), although it should be noted that Attuel's patients may not have been in AF immediately prior to study. AF was also shown to cause progressive enlargement of the atria (93), pointing to an effect of AF on atrial mechanical properties.

Several studies have shown that short-term AF (5–15 min) decreases the atrial refractory period and facilitates subsequent AF reinduction (94–96). These phenomena are greatly attenuated by the L-type Ca^{2+} channel blocker verapamil (95, 96). Although the term remodeling has been applied to these short-term changes, they likely represent functional changes in ion channel behavior and action potential properties that are well known to cause action potential abbreviation with increased cardiac frequency (97). Patients with longstanding AF and atrial flutter show changes in atrial monophasic action potentials typical of remodeling after conversion to sinus rhythm (98), showing that typical remodeling occurs in humans and is a consequence of atrial tachycardia, not AF per se. A recent study shows that abnormalities in atrial refractoriness typical of AF-induced remodeling revert toward normal within 4 days of conversion of very longstanding AF (>5 years mean duration), pointing to the reversibility of remodeling even after long periods of the arrhythmia (66). After electrical cardioversion, recurrence of AF is most likely within the first 5 days (99), an interval consistent with the time required for remodeling to dissipate (14, 66). This observation is consistent with the notion that the changes caused by AF-induced remodeling increase the vulnerability to AF and that, if sinus rhythm can be maintained long enough for the reversal of remodeling, sinus rhythm will be more likely.

CHANGES IN ACTION POTENTIALS AND IONIC CURRENTS IN ATRIAL FIBRILLATION

Changes in Atrial Cellular Electrophysiology Caused by Tachycardia-Induced Remodeling

The prominent changes in atrial refractoriness caused by AF (and atrial tachycardias in general) point to important alterations in the atrial action potential and particularly APD, the principle cellular determinant of the refractory period. Boutdjdir et al showed marked action potential changes in atrial preparations from patients with AF compared with patients in sinus rhythm (100). These alterations, illustrated in Figure 5 (*right*), include a loss of the plateau and decreased APD, as well as increased APD heterogeneity (100). Very similar action potential alterations (Figures 6*A*,*B*) were subsequently observed (101) to develop progressively in dogs as a result of pacing-induced atrial tachycardia (400 bpm). Furthermore,

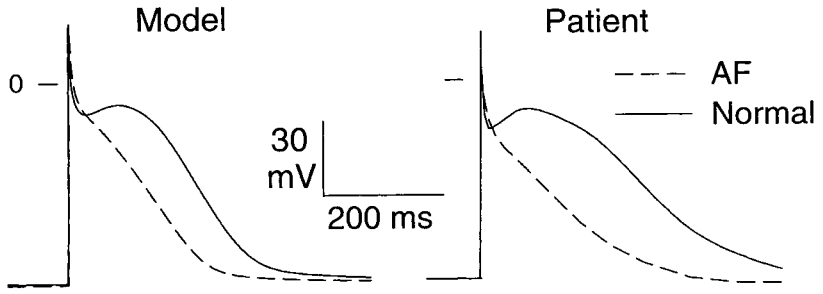

Figure 5 Action potentials from normal human atria (solid lines) and from atria with atrial fibrillation (dashed lines). Results at right are based on experimental data recorded by Boutjdir et al (100), and results at left were obtained with mathematical reconstructions of the human atrial-action potential based on formulations of directly measured ionic currents. The figure is reproduced from Courtemanche et al (108), with permission.

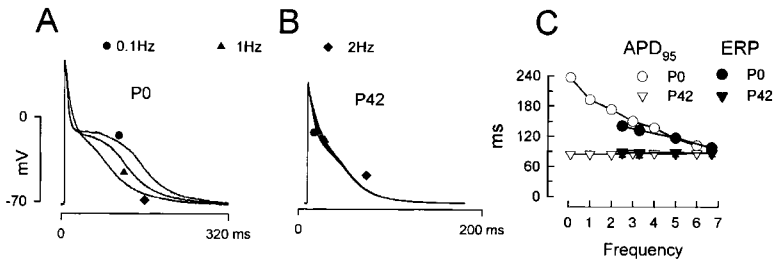

Figure 6 Action potentials recorded at 0.1, 1, and 2 Hz from (*A*) a normal canine atrial myocyte (P0) and from (*B*) a myocyte of a dog atrially paced at 400 bpm for 42 days (P42). (*C*) Mean ± SEM APD_{95} (in isolated cells) and refractory periods (ERP, measured in vivo) in sham (P0) and 42-day rapidly paced (P42) dogs.

pacing-induced APD alterations in isolated cells correspond closely to refractory period changes in vivo (Figure 6*C*), indicating that cellular action potential modifications likely account for the refractory period changes that promote AF. Sustained rapid atrial pacing in dogs was found to cause progressive reductions in L-type Ca^{2+} current ($I_{Ca.L}$) (Figures 7*A*,*B*) and in transient outward K^+ current (I_{to}), without altering delayed-rectifier, ultrarapid-delayed-rectifier (I_{Kur}), or inward-rectifier K^+ currents, Ca^{2+}-dependent Cl^- current, or T-type Ca^{2+} current (101). Current kinetics and voltage dependencies were not altered. The action potential changes caused by rapid pacing (Figures 7*C*,*D*) were mimicked in normal cells by blocking I_{Ca} (Figure 7*E*) and were reversed in cells from rapidly paced dogs by increasing I_{Ca} (Figure 7*F*), suggesting that $I_{Ca.L}$ changes are central to tachycardia-induced atrial action potential abnormalities. The response of the action potential to pharmacological inhibition of I_{to} suggested that I_{to} changes

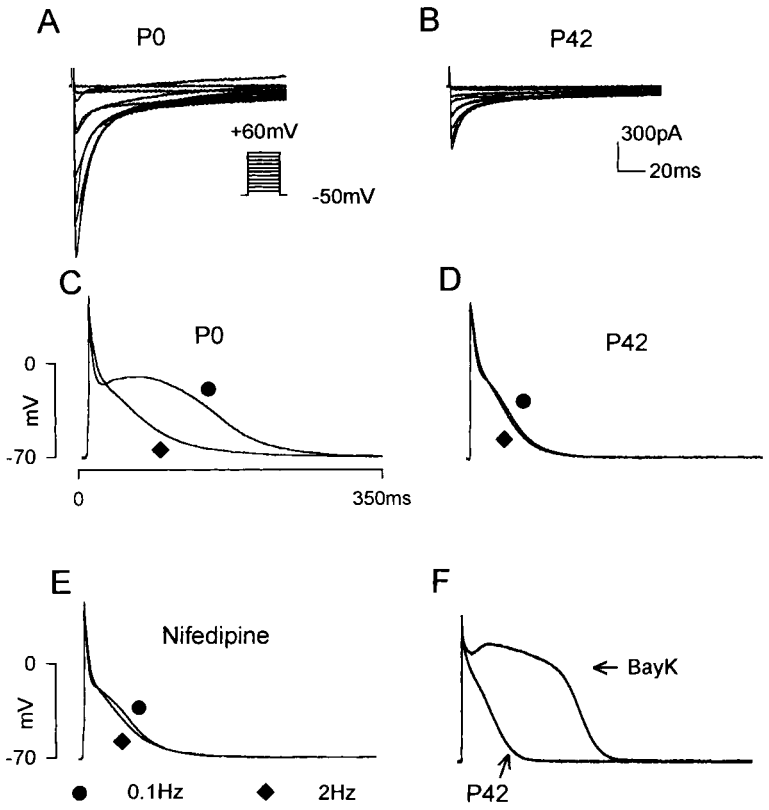

Figure 7 Role of L-type Ca^{2+} current alterations in tachycardia-induced atrial-action potential remodeling. L-type Ca^{2+} currents from representative sham (P0) and 42-day rapidly paced (P42) dog atrial myocytes are shown in *A* and *B.* Action potentials at 0.1 and 2 Hz are shown for P0 and P42 cells in *C* and *D.* Strong $I_{Ca.L}$ inhibition in a P0 cell by 10 μM nifedipine produced action potential changes (*E*) strongly resembling those caused by atrial tachycardia. Increasing I_{Ca} in a P42 cell by exposure to Bay K8644 restored a more normal action potential morphology to a P42 cell.

play a relatively minor role in the action potential changes caused by remodeling (101). Atrial tachycardia also appears to reduce I_{Na} (102, 103), possibly accounting for conduction slowing after prolonged periods of atrial tachycardia (57, 58, 60, 102). In addition to alterations in the steady-state values of APD at different frequencies, AF also affects the dynamics of APD alterations associated with premature beats and with abrupt rate change (104). The modified APD dynamics produced by atrial tachycardia are related to important alterations in Ca^{2+} handling (104, 105), which likely contribute to the transient atrial contractile dysfunction observed after cardioversion of AF (105).

Studies of ionic currents in patients with AF are complicated by the potential effects of concurrent cardiac disease and drug therapy; however, the limited data available are in general agreement with results in animal studies. There is evidence that both I_{to} (106) and $I_{Ca.L}$ (107) are reduced in patients with AF. In addition, I_{Kur} also appears reduced in patients with AF (106). When the ionic current alterations reported in atrial myocytes from patients with AF (106, 107) are incorporated into a mathematical representation of the human atrial action potential based on detailed formulations of directly measured ionic currents (108), the results resemble recorded action potentials closely (Figure 5). Evaluation of the contributions of individual-ionic-current alterations to action potential alterations in the mathematical model suggests that reductions in $I_{Ca.L}$ account for most of the action potential abnormality associated with AF in humans (108), consistent with the data shown in Figure 7.

Observations in Cardiac Conditions that Predispose to Atrial Fibrillation

Studies in patients with conditions associated with AF may give insights into the cellular and ionic abnormalities that lead to the occurrence of the arrhythmia. Action potentials in multicellular atrial preparations from patients with severe atrial disease are depolarized (109) and show a reduced resting potential response to changed $[K^+_o]$ (110), compatible with decreased I_{K1}. Myocytes from dilated human atria show a reduction in APD and an attenuated APD accommodation to rate change (111). Transient outward K^+ current is decreased (111, 112), as is I_{Ca} (111, 113) and, to a lesser extent, the end-pulse outward current related to I_{Kur} (111, 112). The ionic changes seen in cells from patients with chronic AF are not observed in patients with sinus rhythm and a history of paroxysmal AF (106), suggesting that they are a result, and not the primary cause, of the arrhythmia.

Relatively little information is available in the literature about the properties of atrial myocytes in models of cardiac diseases associated with AF. Boyden & Hoffman showed that right-atrial action potential durations were not significantly altered in dogs with right-atrial enlargement from tricuspid insufficiency (114). Similarly, no major atrial action potential property changes were noted in dogs with chronic mitral-valve disease and atrial arrhythmias (45). Right-atrial action potentials were not altered in cats with cardiomyopathy and atrial arrhythmias, but slight APD prolongation was noted in tissue from the more severely dilated left atria (46). We have found that right-atrial APD is not altered at slow rates in dogs with CHF and a substrate for AF, but that APD is increased at rapid rates, consistent with refractoriness alterations (115). CHF decreased I_{to} strongly (by about 50%), and produced smaller but significant decreases in $I_{Ca.L}$ and in the slow component of the delayed rectifier (I_{Ks}) (115). The atrial ionic remodeling caused by CHF differs from tachycardia-induced remodeling in that the latter causes larger decreases in I_{Ca} and has no effect on I_{Ks}. These differences likely explain the different action potential remodeling under the two conditions. The

atrial action potential changes caused by CHF do not obviously account for the substrate for AF produced by CHF, which appears rather to be caused by atrial structural remodeling (48). On the other hand, CHF-induced ionic remodeling has important effects on the electrophysiological milieu in which AF occurs and on the response to antiarrhythmic-drug therapy.

MOLECULAR MECHANISMS ASSOCIATED WITH ATRIAL FIBRILLATION

Molecular Mechanisms of Tachycardia-Related Remodeling

The molecular basis of the atrial electrophysiological remodeling induced by atrial tachycardia is beginning to be unraveled. Dogs subjected to rapid atrial pacing show a progressive reduction in the atrial concentrations of messenger RNA (mRNA) encoding the pore-containing α subunits of L-type Ca^{2+}, Na^{+}, and I_{to} channels (116). Corresponding reductions in Na^{+} and I_{to} channel protein are apparent on immunoblots (116), and atrial dihydropyridine receptor binding (a reflection of the number of L-type Ca^{2+} channels) is also decreased in dogs subjected to atrial tachycardia (117). The mRNA concentrations of clones (DERG and Kir2.1) corresponding to currents (I_{Kr} and I_{K1}) that are unaltered by atrial tachycardia, are unchanged, and there is quantitative agreement between the extent of mRNA downregulation and directly measured changes in $I_{Ca.L}$, I_{to}, and I_{Na} (Figure 8). No change in Na^{+}-Ca^{2+}-exchanger mRNA or protein expression was observed (116). These observations point to decreases in mRNA levels, likely owing to transcriptional downregulation, as the molecular mechanism of tachycardia-induced changes in atrial ionic-current expression.

Recent clinical studies support the relevance to clinical AF of the results of experimental studies on the molecular basis of tachycardia-induced atrial ionic remodeling. Patients with persistent AF have significant decreases (average decrease ranging from 49 to 60%) in mRNA encoding L-type Ca^{2+} channel α_{1c} subunits, as measured by semiquantitative reverse transcriptase-polymerase chain reaction (118–120). Expression levels of Na^{+}-Ca^{2+}-exchanger, calsequestrin, phospholamban, and ryanodine receptor mRNA were unaltered (118–120), but a decrease in sarcoplasmic-reticulum Ca^{2+} ATPase mRNA of variable magnitude has been noted (118, 120). L-type Ca^{2+} channel protein levels were also reduced as measured by slot-blot analysis (120).

The signal transduction pathways responsible for changes in mRNA levels induced by atrial tachycardia are currently unknown. The histological appearance of atrial tissue subjected to several hours of rapid pacing is compatible with Ca^{2+} overload (59), and there is some evidence for a protective effect of Ca^{2+} channel blockers against the consequences of short-term (95, 96) and longer-term (121, 122) atrial tachycardia. $Ca^{2+}{}_{i}$-sensitive pathways may therefore be involved, but

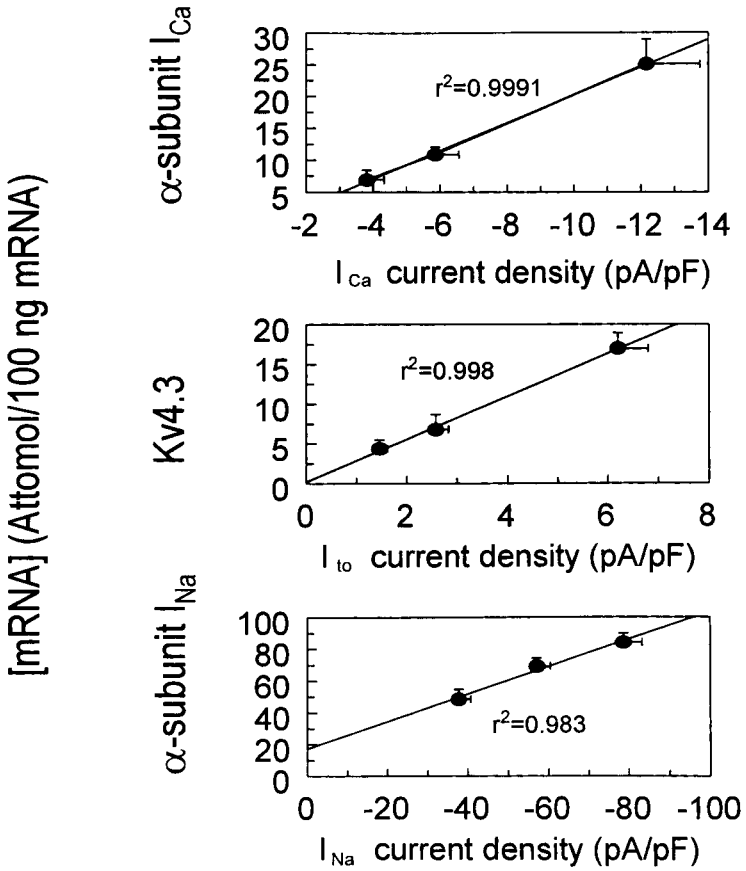

Figure 8 Changes in mRNA concentration as measured by competitive reverse transcriptase-polymerase chain reaction and corresponding ionic current densities measured in atrial tissue from sham dogs and dogs subjected to 7 and 42 days of atrial pacing at 400 bpm. Results are mean ± SEM and best-fit regression lines are shown.

the present evidence is limited, and the precise signaling pathways remain unknown.

Genetic Aspects and Possibility of Molecular Therapeutics

The description of a kindred with genetically based AF (123) has raised exciting new opportunities in the understanding and management of AF. The specific gene involved in familial AF is still unknown, but work is proceeding at a pace that suggests that the molecular basis of familial AF will be known within two years. Recent advances in molecular electrophysiology have provided for exciting new opportunities in arrhythmia management (124). The identification of ion channel

clones that are functionally expressed in the human atrium and not the ventricle, along with the demonstration of specific knockdown of the corresponding current by exposure to antisense oligodeoxynucleotides (125), raises the possibility of chamber-specific antiarrhythmic therapy that would be effective against AF without collateral side effects like ventricular proarrhythmia. Recent demonstrations of the ability of adenoviral gene transfer to knock down cardiac ion channel expression (126) and to alter cellular excitability (127, 128) indicate that the therapy of cardiac arrhythmias by modifying gene expression may become a reality in the foreseeable future.

A PATHOPHYSIOLOGICAL ANALYSIS OF ATRIAL FIBRILLATION AND RELATIONSHIP TO NEW THERAPEUTIC OPPORTUNITIES

Recent advances in our understanding of the pathophysiology of AF provide potential new insights into AF mechanisms, as illustrated in Figure 9, with implications for novel approaches to AF therapy. Atrial ectopic activity can produce

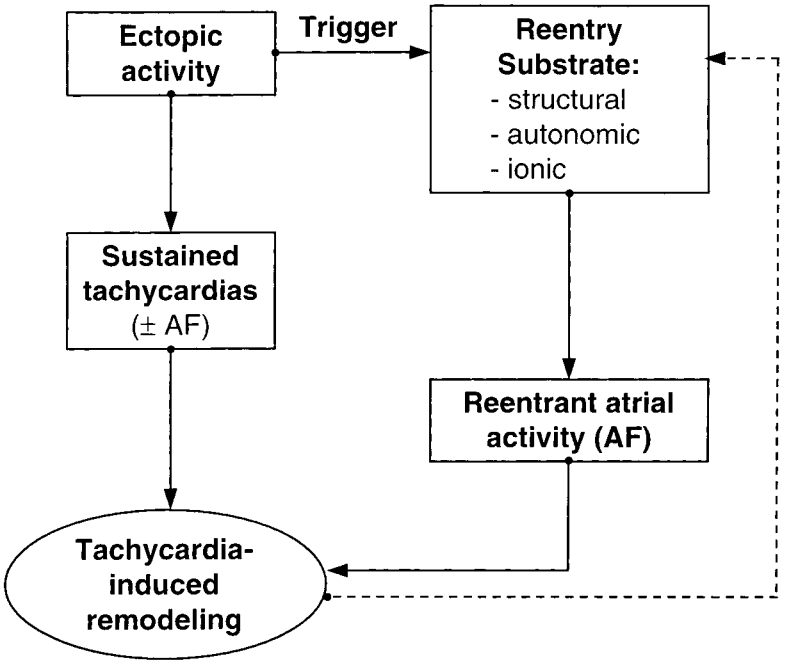

Figure 9 Schematic of mechanisms that can initiate atrial fibrillation and promote its maintenance. Tachycardia-induced remodeling is a final common pathway via which AF caused by any mechanism results in a substrate that favors multiple-circuit reentry and promotes the maintenance of AF.

atrial tachyarrhythmias, which may at times present as very rapid atrial tachycardias and at others as frank AF (15). Ectopic activity can also act as a trigger for a substrate that can maintain reentry, with potential primary substrates including important structural components, as in CHF-related AF (48), autonomic determinants as in vagal AF (37, 38, 40, 41), or ionic determinants (101) such as recurrence of AF in a patient with remodeled atria within 1 or 2 days after electrical cardioversion. Atrial tachycardia resulting either from rapid ectopic activity or from reentrant AF will cause tachycardia-induced remodeling, which will tend to promote the maintenance of AF by favoring multiple-circuit reentry. The pathophysiology associated with AF is thus a dynamic function of the underlying cause(s) and the changes resulting from maintenance of the arrhythmia itself.

This analysis points to potential therapeutic targets other than the traditional ionic currents involved in atrial repolarization. For example, it may be possible to intervene at the level of the signal transduction system that causes AF-promoting structural remodeling. Clinical results point to a beneficial effect of angiotensin-converting enzyme inhibitors in preventing AF after myocardial infarction (129), and we have obtained preliminary data suggesting that converting enzyme inhibitors may prevent AF-promoting structural remodeling in a dog model of CHF (130). If the structural basis for AF results in single-circuit reentry, a single ablation lesion at a critical point in the pathway may be sufficient to prevent the arrhythmia (89). The ablation of ectopic foci that trigger AF may cure AF caused by ectopic focal discharge (15). The development of tachycardia-induced remodeling may be amenable to pharmacological manipulation. For example, the T-type Ca^{2+} channel blocker mibefradil has been found to be highly effective in preventing development of the atrial tachycardia-induced AF substrate in dogs (122). Prevention of AF-induced remodeling could have a variety of beneficial effects (131), including decreasing the resistance of the arrhythmia to antiarrhythmic-drug therapy and decreasing the risks of recurrence following cardioversion. The prompt cardioversion of AF by an implanted device may result in a progressive increase in the interval to the next AF recurrence (132) by preventing remodeling from developing, exemplifying a concept that has become known as “sinus rhythm begets sinus rhythm.” Many other innovative therapeutic approaches are likely to follow our recently improved understanding of fundamental AF mechanisms.

CONCLUSIONS

In retrospect, the insight of researchers in the early twentieth century into AF mechanisms is remarkable. Recent work confirms the accuracy of this early work, while providing deep and sophisticated insights into underlying mechanisms at levels ranging from the molecule to humans. A great deal was known about AF before 1925, but the explosion of new knowledge about the arrhythmia in the last five years has been impressive. This new knowledge will certainly be translated

into important practical advances in arrhythmia management over the next five years.

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