

Review

Atrial electrophysiological remodeling caused by rapid atrial activation: underlying mechanisms and clinical relevance to atrial fibrillation

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Abstract

One of the most exciting developments in our understanding of atrial fibrillation (AF) over the last several years has been the recognition that AF itself modifies atrial electrical properties in a way that promotes the occurrence and maintenance of the arrhythmia, a process termed ‘atrial remodeling’. The principle stimulus for AF-induced atrial remodeling is the rapid atrial rate that results: rapid regular atrial pacing produces changes similar to those caused by AF in animal models. The mechanisms of atrial tachycardia-induced remodeling have been extensively explored, and involve changes in atrial electrophysiology associated with altered ion channel function. The most important ionic change is a reduction in L-type Ca^{2+} current, which reduces action potential duration (APD) and APD adaptation to rate. AF-induced changes in ion channel function appear to be due both to rapid voltage- and time-dependent alterations in channel availability caused by tachycardia and to slower downregulation of messenger RNA concentrations encoding α -subunits of specific ion channels. Atrial remodeling likely contributes importantly to a wide variety of clinical phenomena of previously unrecognized mechanism, including atrial dysfunction after cardioversion of AF, the increasing resistance to therapy of longer-standing AF, the association of AF with other forms of supraventricular tachyarrhythmia and the tendency of paroxysmal AF to become chronic. The present paper reviews the state of knowledge regarding the mechanisms and clinical consequences for AF of atrial remodeling caused by rapid atrial activation. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction and historical overview

Sustained atrial tachycardias, in particular atrial fibrillation (AF), cause changes in atrial electrophysiological function that promote the occurrence and maintenance of AF. This process is often referred to as atrial electrophysiological ‘remodelling’. Awareness of the process and its potential significance burst into the consciousness of cardiac electrophysiologists with the publication of a seminal paper by Wijffels et al. in 1995 [1]. These investigators used a very elegant technique to monitor the cardiac rhythm of chronically-instrumented goats, and to induce AF electrically whenever sinus rhythm was sensed.

As illustrated in Fig. 1, the duration of spontaneously-maintained AF increased progressively over time because of alterations in atrial electrophysiological properties caused by rapid pacing-induced AF. The authors referred to the phenomenon observed as ‘AF begets AF’, a term used subsequently by many authors to describe the context and consequences of atrial electrophysiological remodeling caused by AF.

Prior to Wijffels’ publication, there was substantial evidence pointing to the ability of AF to alter atrial structure and/or electrophysiological function. As early as the 1920s, the importance of AF duration in determining the response to antiarrhythmic drug therapy was recognized [2,3], with longer-standing AF being more resistant to rhythm reversion and more likely to recur over time

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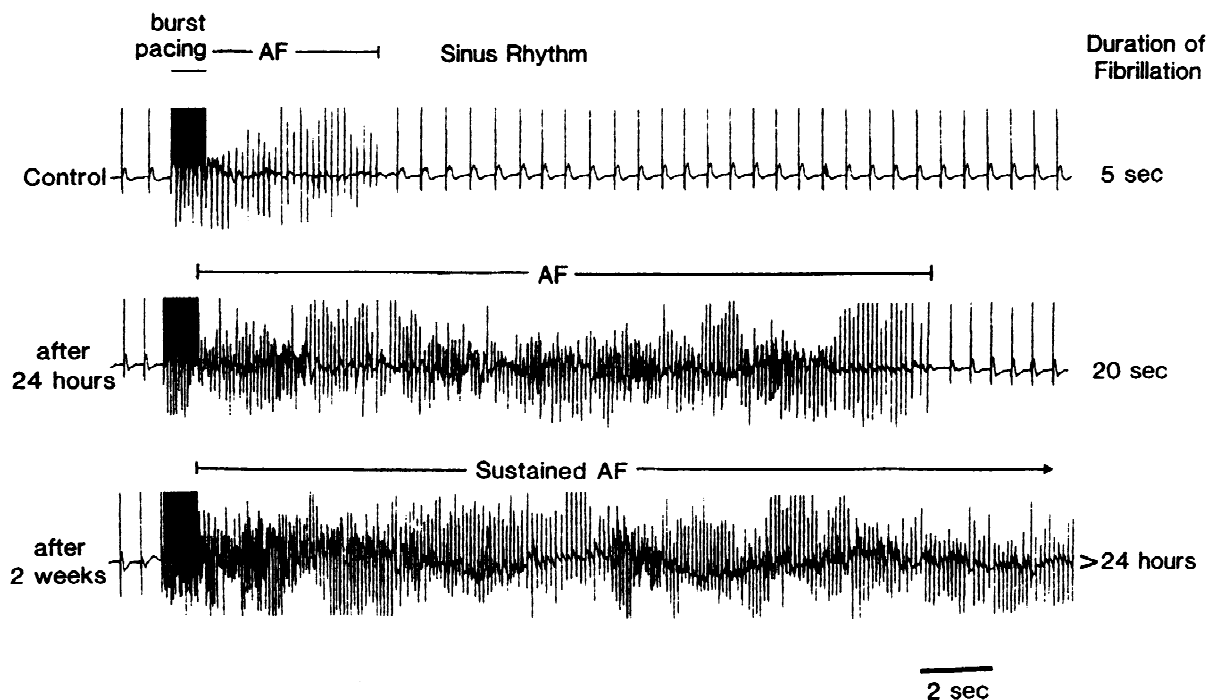


Fig. 1. Duration of AF induced by electrical burst pacing in a chronically instrumented goat after AF had been maintained for the durations indicated to the left of each panel (reproduced from Ref. [1], by Wijffels et al., with the permission of the American Heart Association).

(Fig. 2). Atrial enlargement is well-known to be associated with AF, and is usually considered to contribute to arrhythmia maintenance by increasing the atrial mass. Sanfilippo et al. showed that patients with AF tend to develop progressive atrial dilation [4], suggesting an effect of AF on atrial mechanical properties and that the recognized association between atrial dilation and AF may be due to AF-induced dilation as well as to the ability of atrial dilation to promote AF. It has long been noted by clinicians that the natural history of AF often involves episodes of paroxysmal arrhythmia followed by chronic AF, suggesting that the occurrence of AF may alter atrial properties to increase the probability that the arrhythmia is

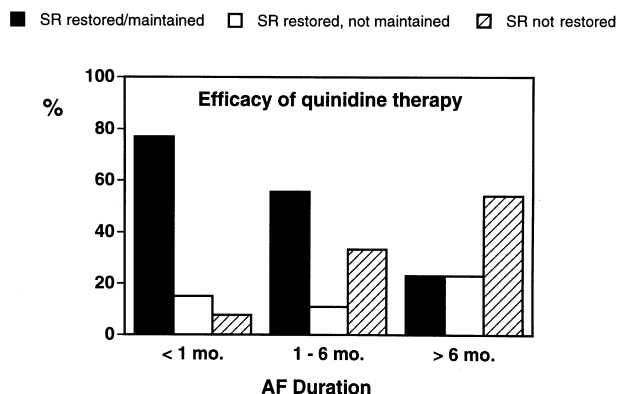


Fig. 2. Relationship between the duration of AF symptoms preceding therapy and the success of quinidine therapy in producing maintained sinus rhythm in the study of Parkinson and Campbell published in 1929 [3].

sustained indefinitely, a process termed by Rosenbaum the ‘domestication of AF’ as quoted by Wijffels et al. [1]. Finally, an abstract published in 1985 indicated that when AF was maintained by electrical stimulation for several weeks in dogs, it often sustained itself spontaneously when electrical stimulation was discontinued [5]. The critical contribution of Wijffels and co-workers was to recognize the significance of the phenomenon and to demonstrate it in an elegant experimental model relevant to clinically observed ‘domestication of AF’. The importance of this work cannot be overstated— it led to the first reliable and highly reproducible animal model with a stable substrate for sustained AF, and to important novel concepts about the pathophysiology of the arrhythmia. Experimental work on AF mechanisms has increased rapidly subsequent to, and largely as a result of, the Wijffels paper. Many of these experimental studies have used rapid 1:1 atrial pacing to create a substrate that can support AF, since regular atrial activation at rates ≥ 400 /min produces many of the electrophysiological changes caused by pacing-induced AF [6–9].

2. Mechanisms of AF-induced remodeling

2.1. Changes in electrophysiological properties in vivo

Over the past several years, AF-induced remodeling and its underlying mechanisms have been studied in substantial detail. The same year that the Wijffels paper was pub-

lished, Morillo et al. [6] showed that rapid atrial pacing (400 bpm) strongly promotes the ability to maintain AF in dogs, with changes quite similar to those observed by Wijffels et al. [1]. This has led to the notion that AF-induced remodeling is primarily due to the rapid atrial activation rates caused by AF, an idea supported by a subsequent study by Wijffels et al. [7]. Consequently, many investigators have used rapid atrial pacing in experimental models to study the electrophysiological changes caused by sustained atrial tachycardia, hoping to gain insights into the atrial electrophysiological changes caused by rapid atrial activation due to AF in man.

Virtually all studies have shown that sustained atrial tachycardia decreases atrial effective refractory period (ERP). ERP changes occur over a period of days to weeks [1,6,8,9], but AF can decrease ERP over a time interval as short as several minutes [10]. Decreases in ERP promote AF by decreasing the wavelength (distance traveled by the electrical wave during the ERP, which determines the minimum path length that can support reentry), thereby allowing the atria to accommodate a larger number of functional reentry circuits and decreasing the chance of spontaneous termination [11,12]. Although the ERP reduction caused by AF favours arrhythmia maintenance, it cannot be the only factor involved because AF-induced ERP alterations become maximal well before AF-promoting effects stabilize [1,9,13]. Atrial conduction slowing also appears to be caused by atrial tachycardia [6,8,9], and has a slower time course than ERP changes, potentially accounting for at least a part of the continued development of AF promotion after ERP changes have stabilized [9].

In addition to changes in the absolute value of ERP, atrial tachycardia alters the frequency-dependence and spatial distribution of ERP in potentially important ways. A reduction in the rate adaptation of the ERP is a finding characteristic of tachycardia-induced atrial remodeling [1,9], and is also observed in patients with AF [14,15]. The loss of rate adaptation is such that ERP decreases caused by AF are maximal at slower rates (like those of sinus rhythm) and minimal at rapid rates (such as during AF). It is hard to understand how lack of ERP rate adaptation can contribute to the promotion of AF maintenance, since it minimizes the ERP reduction during rapid rates such as those of AF. On the other hand, the ability of premature beats to induce AF appears to be critically determined by ERP values at slow rates like those of sinus rhythm [16,17]. Thus, interventions (like loss of rate adaptation) which decrease ERP at slower rates favour the induction of AF by premature beats, whereas interventions that increase ERP at slow rates prevent AF induction [17]. Since AF is typically initiated by premature atrial extrasystoles [18], the decreased ERP rate adaptation caused by AF likely contributes by enhancing the vulnerability to AF induction by premature beats [14].

The spatial heterogeneity of atrial ERP appears to be an important determinant of the ability of AF to maintain

itself [16,19–22]. Direct measurement of the ERP during AF is difficult. The AF cycle length can be used as an index of atrial refractoriness during AF, and the spatial variability in AF cycle length is an index of the heterogeneity of refractoriness during AF [23]. The spatial variability in AF cycle length increases over time in dogs subjected to rapid atrial pacing, and this index of the heterogeneity of refractoriness during AF is a significant statistical predictor of atrial tachycardia-induced changes in AF duration [9]. Recent studies suggest that changes in atrial ERP caused by sustained atrial tachycardia are spatially variable, both among and within different atrial regions, resulting in an increased ERP heterogeneity that contributes importantly to the AF-promoting effects of atrial remodeling [22].

The combination of electrophysiological changes caused by sustained atrial tachycardia – reduced ERP, slowed conduction and increased spatial ERP heterogeneity – would be expected to promote AF maintenance by increasing the number of functional reentry circuits during AF. Evidence to support this contention has been obtained in epicardial mapping studies, which point to an increased number of functional circuits during AF in dogs subjected to chronic rapid atrial pacing [9].

2.2. Underlying cellular mechanisms

Reductions in ERP and in ERP adaptation to rate are characteristic features of tachycardia-induced atrial electrical remodeling. Standard microelectrode studies of human atrial preparations show a reduction in APD and in APD rate adaptation [15], pointing to APD changes as the mechanism for ERP alterations caused by AF. A direct comparison between ERP changes caused by rapid atrial pacing in dogs and APD changes in atrial myocytes isolated from the same animals [24] lends further support to the idea that alterations in ERP caused by atrial tachycardia are due to changes in APD (Fig. 3).

An examination of ionic current changes in atrial myocytes from control dogs and dogs subjected to rapid atrial pacing [24] indicates that a variety of currents are unchanged, including inward and delayed rectifier K^+ currents, T-type Ca^{2+} current and Ca^{2+} -dependent Cl^- current. Currents that show important alterations are the transient outward K^+ current (I_{to}) and L-type Ca^{2+} current (I_{Ca}), both of which are reduced by about 70% after 6 weeks of rapid atrial pacing. Other properties of I_{Ca} and I_{to} , like voltage, time and frequency dependence are unchanged [24]. This observation suggests that the changes observed are due to a reduction in the number of functional channels in the membrane rather than to a change in basic channel properties. The use of pharmacological probes to mimic the effects of reduced I_{Ca} and I_{to} on the action potential suggests that reductions in I_{Ca} likely play a central role in the APD alterations caused by atrial tachycardia, with the changes in I_{to} being of much less

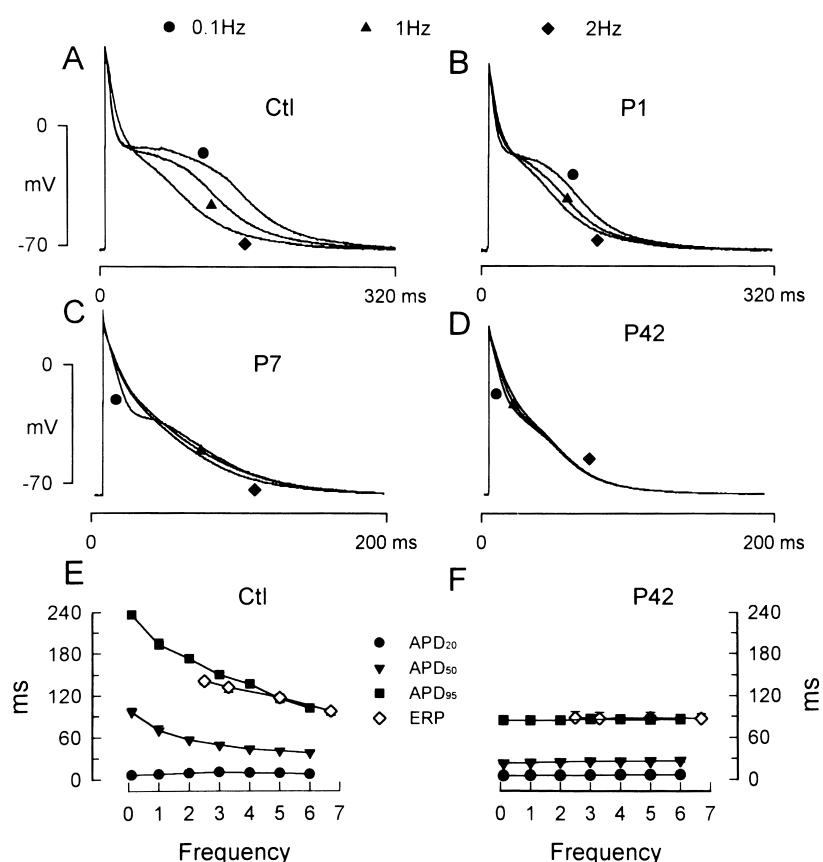


Fig. 3. Top and middle: Action potential changes in atrial cells obtained from dogs subjected to atrial pacing at 400/min for 1 (P1), 7 (P7) or 42 (P42) days, compared to a cell from a sham-instrumented dog (Ctl). Bottom: Rate-dependence of APD (to the percentage of repolarization indicated) measured in isolated atrial cells in vitro, along with atrial effective refractory period measured in vivo, for sham-instrumented dogs (E) and 42-day paced dogs (F). These results show that rapid atrial pacing in vivo causes progressive action potential changes in isolated atrial myocytes, particularly reduced APD and decreased APD adaptation to rate. Furthermore, the agreement between APD changes in vitro and ERP values in vivo (bottom panels) indicates that the properties of isolated cells agree well with in vivo behaviour, and that APD changes are likely responsible for the ERP alterations observed in the intact animal. Furthermore, this agreement suggests that ionic current measurements in isolated cells are likely relevant to mechanisms underlying electrophysiological changes in vivo (from Ref. [24], with the permission of the American Heart Association).

importance (Fig. 4), despite the quantitatively similar reduction (about 70%) of I_{Ca} and I_{to} . Studies of human atrial myocytes suggest that AF in man is associated with alterations in I_{to} [25] and I_{Ca} [26] very similar to those noted in the rapid-pacing dog model.

Studies of I_{Na} in atrial myocytes of dogs subjected to rapid atrial pacing indicate a progressive reduction in current density over time [27]. The time course of changes in current density parallel those in conduction velocity [27], suggesting that alterations in I_{Na} amplitude contribute to the conduction changes associated with sustained atrial tachycardia.

Changes in intercellular electrical connections could play a role in AF-induced remodeling. The data presented to date are contradictory. Elvan et al. showed an increase in connexin43 protein in dogs with AF [28]. On the other hand, van der Velden et al. showed no change in connexin43 and an alteration in the distribution of connexin40 in goats with AF [29].

2.3. Changes in ultrastructure and Ca^{2+} handling

In addition to electrophysiological changes, AF causes alterations in cellular ultrastructure and Ca^{2+} handling. Mitochondrial enlargement, glycogen accumulation, loss of sarcoplasmic reticulum and degeneration of contractile elements have been noted in the atria of goats subjected to chronic AF, changes resembling those observed in hibernating myocardium [30]. Abnormal Ca^{2+} handling has been noted in dogs subjected to rapid atrial pacing (400 bpm) for 1 week or longer [31]. The intracellular systolic Ca^{2+} transient (reflecting Ca^{2+} release during the action potential) is reduced in atrial myocytes from such animals, with the reductions becoming more marked as activation frequency increases. The rates of Ca^{2+} release and reuptake are decreased and there is a marked negative staircase of the Ca^{2+} transient, compatible with abnormalities in Ca^{2+} cycling. This negative force–frequency relation is similar to that observed at the ventricular level in the

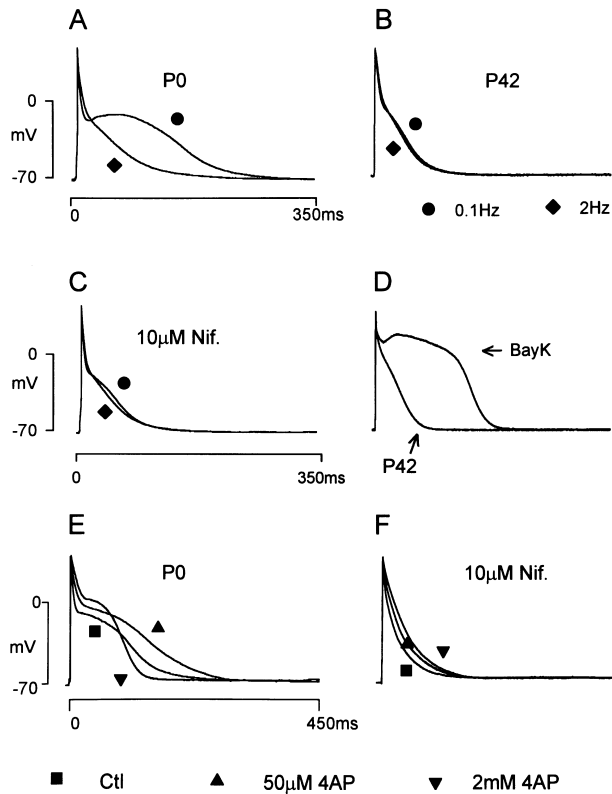


Fig. 4. Action potentials at 0.1 (circles) and 2 Hz (diamonds) in an atrial myocyte from a sham dog (A) and from a 42-day paced dog (B). (C) Action potentials from a sham dog atrial cell in the presence of the I_{Ca} blocker nifedipine, which mimicked the result of chronic rapid pacing. (D) The I_{Ca} agonist BayK 8644 was able to restore the action potential plateau of a cell from a 42-day paced dog. (E) 4-Aminopyridine (4AP) did not reproduce the effects of rapid pacing in a cell from a sham dog at concentrations that block only the ultrarapid delayed rectifier, I_{Kur} (50 μ M) or that block I_{Kur} and I_{to} (2 mmol/l). (F) In a control cell exposed to nifedipine to mimic the effects of I_{Ca} depression, concentrations of 4AP that inhibited both I_{Kur} and I_{to} (2 mmol/l) had no significant additional effect compared to concentrations inhibiting only I_{Kur} (50 μ M). These results suggest that I_{Ca} suppression, and not I_{to} reduction, is the main factor responsible for action potential changes caused by chronic atrial tachycardia (from Ref. [24], with the permission of the American Heart Association).

presence of heart failure. Cellular contractility is decreased in parallel with the reduction in systolic Ca^{2+} release (Fig. 5), suggesting cellular contractile abnormalities caused by impaired Ca^{2+} transients; however, a degree of contractile dysfunction remains even when the Ca^{2+} transient is normalized by increasing extracellular $[Ca^{2+}]$ [31]. The incomplete recovery of contractility when the Ca^{2+} transient is normalized suggests a contribution to contractile dysfunction of other mechanisms in addition to reduced Ca^{2+} release during the action potential.

2.4. Signalling pathways involved in remodeling

The signalling pathway(s) by which AF leads to atrial remodelling are incompletely understood. Activation of

ATP-dependent K^+ channels and intact autonomic nervous system function do not appear to be essential, and acute cardiac volume loading does not reproduce the electrophysiological changes caused by sustained AF [7]. On the other hand, rapid atrial pacing causes changes that closely mimic the alterations caused by AF, suggesting that atrial tachycardia is the principle stimulus for AF-induced remodeling [7]. Several lines of evidence point to a role of cellular Ca^{2+} overload in tachycardia-induced remodeling. Histological changes compatible with Ca^{2+} -overload induced injury have been noted in atria that were rapidly paced for several hours [32]. ERP abbreviation and AF promotion caused by short-term (5 to 15 min) of AF can be limited by the L-type Ca^{2+} channel blocker verapamil [33,34], as can contractile dysfunction due to brief tachycardia [35]. Verapamil also attenuates the ERP changes caused by 24 h of atrial tachycardia in the goat, although AF promotion does not appear to be importantly affected [36]. Recently completed work suggests that T-type Ca^{2+} channels may be important in mediating atrial tachycardia-induced remodeling, because the selective T-type Ca^{2+} channel blocker mibefradil limits both the ERP changes and AF promotion caused by one week of rapid atrial pacing [37]. The similarity between the cellular ultrastructural changes caused by sustained AF and those seen in hibernating myocardium [30] have led to a suggestion that atrial ischemia may play a role in triggering remodeling caused by AF. A potential role for atrial ischemia is consistent with the protective effect observed with a proton-pump inhibitor in short-term tachycardia-induced atrial remodeling [38]. Alternatively, inhibition of Na^+ , H^+ -exchange (proton pump) may alter cellular ionic homeostasis and combat Ca^{2+} overload.

The precise role of cellular Ca^{2+} loading in initiating tachycardia-induced remodeling changes is poorly understood, as is the potential involvement of alternative or subsequent initiating signals. However, it is known that atrial tachycardia produces discrete changes in cardiac gene expression [39]. Specifically, messenger RNA (mRNA) encoding the α -subunits of cardiac L-type Ca^{2+} , Na^+ and I_{to} channels is downregulated, with the time course and magnitude of changes in mRNA concentration paralleling those in corresponding current density. The mRNA levels corresponding to currents that are unaffected by tachycardia-induced remodeling, like I_{Kr} and I_{K1} , are unaltered. These observations indicate that changes in cardiac gene expression are responsible for the ionic and cellular electrophysiologic abnormalities caused by tachycardia-induced remodeling.

2.5. Temporal issues: AF-induced remodeling as a series of processes

There has been a tendency to think of AF-induced remodeling as a single, discrete process; however, there is

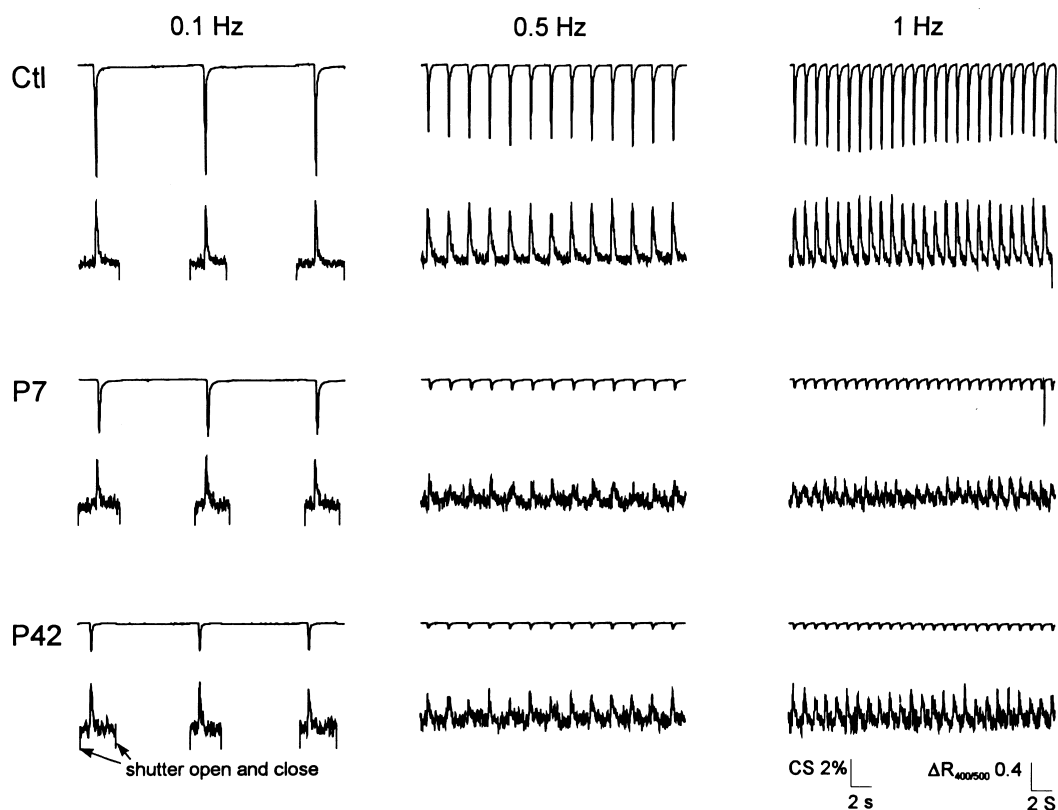


Fig. 5. Changes in atrial cellular contractile strength (CS, shown by the cell shortening recordings, with downward deflections indicating contraction, in the top of each panel; scale indicated by CS at bottom right) and intracellular Ca^{2+} transients (bottom of each panel, upward deflections indicate increased free cytoplasmic $[\text{Ca}^{2+}]$; scale indicated by $\Delta R_{400/500}$ at bottom right) caused by sustained atrial tachycardia. Results are shown for one cell from a sham dog (Ctl), one from a 7-day paced dog (P7) and one from a 42-day paced dog (P42) at each of the frequencies indicated. Atrial tachycardia caused a progressive decrease in the amplitude of the Ca^{2+} transient, which paralleled and partially accounted for an important decrease in contractile function. Changes were more marked at faster rates. The results of this study indicated that sustained rapid atrial firing causes a tachycardia-induced atrial myopathy, which is largely (but not exclusively) due to abnormal intracellular Ca^{2+} release (from Ref. [29], reproduced with permission of the American Heart Association).

no persuasive evidence for this contention. On the contrary, there are good reasons to believe otherwise. Abrupt increases in frequency are well-known to cause immediate (within one action potential) and then gradual (reaching steady state over several minutes) decreases in APD [40,41]. These alterations in APD reduce ERP and shorten the wavelength for reentry, which will facilitate the occurrence and maintenance of reentrant arrhythmias like AF. The rapid nature of these changes suggests that this short-term APD adaptation to rate is due to functional changes in ion channels and transporters. Experimental data point to an important role of L-type Ca^{2+} current in short-term rate adaptation of human atrial APD [42], and a mathematical model of the human atrial action potential suggests that both voltage-dependent and intracellular Ca^{2+} -induced inactivation of I_{Ca} contribute to rate-induced APD abbreviation [43]. Thus, brief periods of AF (<1 h) would be expected to abbreviate ERP and favour AF induction via functional changes, including Ca^{2+} -induced I_{Ca} inactivation, that cause APD shortening, potentially accounting for clinical observations of the effects of relatively brief periods of AF [33,34]. Whether this phe-

nomenon should rightly be termed ‘remodeling’, which seems to imply a more permanent change, is debatable; however it has been so designated in the literature [33,34] and the refractoriness abbreviation and AF facilitation induced by several minutes of atrial tachycardia resemble qualitatively changes caused by longer periods of AF.

With longer periods of sustained atrial tachycardia, changes develop over the course of hours to days and their reversal may require up to 24 h after the cessation of tachycardia [1,8,9]. These alterations appear to involve alterations in ion channel density that are due to modified gene expression [24,39]. Furthermore, the time courses of these changes vary, with reductions in ERP, rate adaptation of ERP, I_{Ca} and I_{to} achieving steady state more rapidly than changes in I_{Na} , conduction and AF duration [1,9,24]. Both I_{Ca} inactivation and downregulation of α_{1c} subunits of the L-type Ca^{2+} channel serve to reduce Ca^{2+} entry at the rapid rates of AF. Thus, tachycardia-induced remodeling may include a series of changes, involving rapid functional alterations and slower changes in gene expression, that cause APD reduction and reduced cellular Ca^{2+} loading (Fig. 6). Teleologically, these changes can be

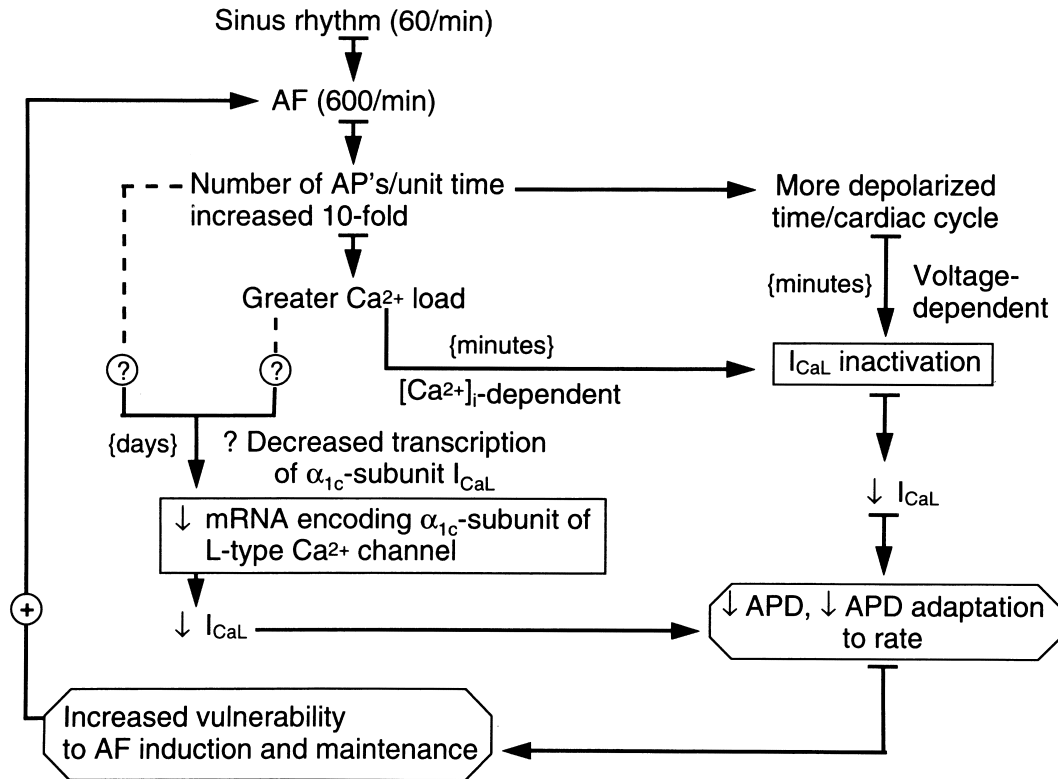


Fig. 6. Schematic illustrating the way in which rapid atrial activation results in both rapid (over minutes) functional reductions in I_{Ca} and slower (over days) genetically determined changes. The signals which mediate the tachycardia-dependent decrease in I_{Ca} mRNA are presently unknown, although cellular Ca^{2+} overload may play a role. Atrial tachycardia causes increased cellular Ca^{2+} loading, which if unchecked could threaten cell viability. The Ca^{2+} -loading effects of tachycardia are limited by the rapid and slower I_{Ca} -reducing mechanisms shown, but at the cost of electrophysiological changes (especially reduced APD and rate-adaptation of APD) which promote AF initiation and perpetuation.

considered to reduce I_{Ca} and thereby protect the cell against potentially-lethal Ca^{2+} overload resulting from an almost 10-fold increase in the rate of action potential generation between resting sinus rhythm and AF. This protective effect occurs, however, at the expense of electrophysiological changes that promote the maintenance of AF.

3. Clinical consequences

3.1. Insights into clinical occurrence of AF

A number of the features of clinical AF occurrence may be related to rate-dependent atrial remodeling. For example, it is well-known that chronic AF is often preceded by episodes of paroxysmal AF. It has been suggested that electrophysiological changes produced during AF paroxysms may favour the perpetuation of the arrhythmia, promoting the transition from the paroxysmal to the sustained form (or 'the domestication' of AF) [1]. A variety of atrial tachyarrhythmias, including atrial flutter and AV reentrant tachycardias associated with the Wolff–Parkinson–White syndrome, are associated with AF. It is quite conceivable that these atrial tachyarrhythmias cause

atrial remodeling that promotes their degeneration into AF. In fact, atrial flutter has been shown to induce electrical remodeling in man like that caused by AF [44].

The resistance of longer-duration AF to therapy was recognized in the 1920s [2,3], when it was noted that the ability of quinidine therapy to restore and maintain sinus rhythm in patients with AF is strongly related to the duration of the arrhythmia before treatment (Fig. 2). More recent studies have confirmed the great importance of AF duration in determining the response to a variety of antiarrhythmic drugs [45–47]. The duration of atrial fibrillation or flutter is also an important predictor of the restoration of sinus rhythm by direct current cardioversion [48]. These observations may well result from the atrial electrophysiological changes, which promote AF, that result from the arrhythmia itself. In fact, recently-presented preliminary findings indicate that a smaller dose of an antiarrhythmic drug is necessary to convert sustained AF following 24 h of electrically maintained AF in a goat model compared to AF that had been maintained ≥ 1 week [49]. Interestingly, soon after drug-induced cardioversion, AF vulnerability remains high in hearts remodeled by AF, with single premature beats readily reinducing the arrhythmia [50]. AF recurrence after electrical cardioversion appears to be particularly likely in the immediate (i.e., 1 to

2 days) post-cardioversion period [51]. This may reflect the time required for reversal of AF-induced remodeling [1], suggesting that if patients can be kept in sinus rhythm over this critical period the chance of maintaining sinus rhythm may be greatly increased.

3.2. Implications for the termination of AF and maintenance of sinus rhythm

As mentioned in Section 3.1, longer-duration AF is more resistant to conversion by antiarrhythmic drug therapy [2,3,44–47]. In some patients, this may simply reflect a greater degree of atrial pathology- i.e., if atrial pathology is more severe, AF is likely to be sustained for longer periods, and is also likely to be more difficult to terminate. On the other hand, given the substantial time-related changes in atrial electrophysiology caused by tachycardia-induced remodeling, it is also quite conceivable that these changes caused by AF itself confer some degree of drug resistance. The precise mechanisms for the drug resistance conferred by AF-induced remodeling are an interesting and as yet unresolved issue. Theoretical analyses suggest that the ionic remodeling induced by AF may modify the response to K^+ channel blocking antiarrhythmic agents [52]. In addition, the changes in the AF substrate itself may be quite significant – i.e., if the wavelength for reentry is substantially reduced by AF [9], it will require that much more drug-induced wavelength prolongation to terminate the arrhythmia.

In addition to making drug conversion of AF more difficult, AF-induced remodeling may also have consequences for the maintenance of sinus rhythm. There is evidence that AF recurrence is most likely immediately after conversion to sinus rhythm, and that the recurrence rate decreases steeply after several days [51], a time course consistent with that of recovery from AF-induced remodeling [1]. It may prove useful to target more intensive drug therapy to the days or week following conversion of AF, in order to prevent these early recurrences, and then to provide less intense drug therapy to allow for maintenance of sinus rhythm with a reduced risk of adverse effects. An additional approach which may prove interesting is the use of drug therapy to reduce directly the electrophysiologic consequences of AF-induced remodeling. There are data which suggest that Ca^{2+} channel blockade of L- [36] and/or T- [37] type Ca^{2+} channels may have some value in this regard. Conversion of AF to sinus rhythm as soon as possible after AF onset might also be useful, but is often limited in clinical practice by the risk of thromboembolism upon AF conversion if AF has lasted for over 48 h in patients not on anticoagulants [53]. The implantable atrial defibrillator might be of value in this regard for some patients, by virtue of its ability to detect and convert AF soon after its onset. Preliminary results with the implantable defibrillator suggest that the interval to recurrence of

AF is progressively increased by the device, consistent with a beneficial effect due to reversal of remodeling [54].

3.3. Implications for understanding atrial stunning after conversion of AF to sinus rhythm

It is well-known that the return of atrial transport function is delayed after AF conversion [55,56]. The delayed return of atrial contraction is associated with a delayed return of physical capacity [56] and may promote the occurrence of thromboembolic events several days or more after cardioversion [57,58]. This atrial ‘stunning’ has been attributed to the DC shock used for cardioversion [57]; however, pharmacologic conversion of AF is also followed by delayed recovery of atrial mechanical function [59,60] and DC shock applied in the absence of AF does not appear to cause atrial contractile abnormalities [61]. Thus, although reversible atrial contractile abnormalities after cardioversion have often been attributed to effects of the intervention used to restore sinus rhythm, there is reason to believe that chronic AF may itself alter atrial cellular contractile properties. This AF-induced contractile dysfunction can only be observed when sinus rhythm is restored, permitting coordinated atrial contraction.

Leistad et al. have shown that short periods of AF (<15 min) impair atrial contractility [62], and that Ca^{2+} loading may be important in this phenomenon [35]. Recent work [31] suggests that remodeling induced by atrial tachycardia (via rapid atrial pacing in dogs) impairs cellular Ca^{2+} handling, reducing the Ca^{2+} transient and thereby reducing cellular contractility (Fig. 5). The reduction in the Ca^{2+} transient is likely due, at least in part, to reduced entry of Ca^{2+} through down-regulated L-type channels, presumably resulting in decreased releasable Ca^{2+} stores. The role of other components of Ca^{2+} handling, including sarcoplasmic reticulum function, ryanodine receptors, Ca^{2+} pumps and Na^+ , Ca^{2+} -exchange has not been established. When the Ca^{2+} transient of rapidly-paced dogs is normalized by increasing extracellular $[Ca^{2+}]_o$, cellular contraction improves substantially; however, some contractile abnormality remains, suggesting the presence of additional factors reducing contractility in the remodeled atria [31]. Detailed ultrastructural studies have been performed in goats with AF-induced remodeling [30]. Over half of the atrial myocytes showed important changes at the cellular level, including myolysis, fragmentation of the sarcoplasmic reticulum, and loss of myofibrils. These contractile element abnormalities likely contribute to the component of contractile dysfunction over and above the reduced Ca^{2+} transient. These observations regarding the effects of remodeling on atrial contractile components and function suggest that tachycardia-induced atrial remodeling is sufficient to produce reversible atrial contractile dysfunction that would manifest as atrial ‘stunning’ after cardioversion. In the dog model, cellular contractile and Ca^{2+} handling abnormalities caused by atrial tachycardia were the same

whether or not sustained AF developed during chronic atrial tachypacing [31], suggesting that contractile dysfunction is due to atrial tachycardia and not AF per se. This concept is compatible with the clinical observation that atrial flutter also produces atrial stunning [63].

4. Important unresolved issues

Despite the important insights that have been obtained into the mechanisms underlying remodeling caused by AF and its clinical consequences, many issues remain unresolved. In addition, research on AF-induced remodeling has raised a variety of new questions that need to be addressed. Some, but by no means all of these, are presented briefly below.

4.1. Rate-sensitive pathways governing cardiac gene expression

Rapid atrial activation clearly leads to a reduction in the density of several cardiac currents [24]. These changes appear to be caused by a reduction in mRNA concentration of the respective channel α -subunits [36], presumably as a result of transcriptional downregulation. Preliminary data suggest that L-type Ca^{2+} channel mRNA levels are also reduced in patients with established AF [64]. These observations suggest that heart rate is an important regulator of the expression of genes encoding cardiac ion channels, and possibly other cardiac proteins as well. It would be important to know whether rate controls ion channel expression directly, e.g. via the accumulation or depletion of critical ionic species, or whether indirect consequences of rate, such as hemodynamic consequences, changes in energy needs (possibly including relative ischemia), neurohormonal changes, or other factors are involved. There is evidence for intracellular $[\text{Ca}^{2+}]$ loading as a potentially important determinant of atrial tachycardia-induced remodeling; however, most of this evidence is indirect. Direct evidence regarding $[\text{Ca}_i^{2+}]$ changes caused by atrial tachycardia is needed, as is information regarding the potential Ca^{2+} -sensitive intracellular processes that lead to tachycardia-induced changes in gene expression and in phenotype. Finally, it is possible that the altered atrial activation pattern associated with atrial pacing and AF may contribute to remodeling – this possibility remains to be assessed in future work.

4.2. What initiates AF in the first place?

The phenomenon of AF-induced remodeling provides insights into the factors that maintain AF and can help to convert it from a paroxysmal to a sustained arrhythmia;

however, something has to initiate AF and permit it to be maintained long enough to ‘beget’ itself. At the moment, we have relatively little information about the factors that cause AF to begin in the first place. A variety of entities, including congestive heart failure, mitral valve disease, hypertension, coronary artery disease, thyrotoxicosis and the post-cardiac surgery state, promote the occurrence of AF. How they do so is largely unknown. Recent studies suggest that experimental heart failure in dogs causes important atrial structural remodeling, including intense fibrotic changes that cause local conduction disturbances and permit the induction of sustained AF by burst pacing in over 50% of animals [65]. The associated electrophysiologic changes and cellular and ionic alterations are quite different from those observed in the atrial tachycardia model [24,65,66]. Furthermore, the atrial histological changes associated with AF promotion by experimental heart failure resemble those observed in cats with cardiomyopathy [67], dogs with mitral valve disease [68], patients with mitral disease [69,70] and the elderly [71], conditions associated with a predisposition to AF. Recent work from Dr. Haissaguerre’s laboratory suggests that ectopic atrial foci in the pulmonary vein region can cause atrial tachycardias that lead to AF [72]. Further work needs to be performed in both clinical and experimental models in order to elucidate the factors leading to AF initiation. The knowledge gained may help to devise strategies that can be used to prevent the occurrence of AF by countering the development of the substrate that initiates the arrhythmia, rather than simply trying to deal with the arrhythmia when it occurs.

5. Conclusions

The concept of AF-induced electrical remodeling has provided important new insights into mechanisms underlying the arrhythmia. These insights have both theoretical and practical value, and will undoubtedly translate into improved strategies for AF management in the near future. Important issues remain to be addressed, including the nature of the signalling pathways that are engaged by tachycardia and result in altered ion channel expression and the mechanisms by which a variety of pathologies lead to AF initiation in the first place.

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