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REVIEW

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Remodeling of cardiomyocyte ion channels in human atrial fibrillation

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Abstract This review is focused on electrical adaptational processes in patients with chronic AF. Cellular electrical remodeling includes shortening of action potential duration and effective refractory period that can be explained by concomitant alterations in ion channel activity. While most currents studied are reduced or unaffected, the inward rectifier I_{K1} is increased in amplitude. The time courses of these changes and the putative molecular mechanisms suggest that electrical remodeling in chronically fibrillating human atria are adaptive processes. New therapeutic options could consist of supporting rather than reversing the adaptive mechanisms.

Key words Atrial fibrillation – ion channels – molecular mechanisms

Introduction

Atrial fibrillation (AF) is currently the most common arrhythmia in clinical practice with an increased prevalence in the aged population (100). Pharmacological or electrical conversion to normal sinus rhythm (SR) is not always possible, but even if successful, patients are less likely to remain in SR the longer their AF had already persisted (24, 82). In the beginning, episodes of AF terminate spontaneously (paroxysmal AF); however, with increasing duration of the rhythm disturbance, AF proceeds to become "persistent" when converting into SR only by pharmacological or electrical intervention, and eventually becomes "permanent" when SR can no longer be restored at all (3). Experimentally, bursts of rapid atrial pacing induce AF and promote the perpetuation of AF. This has been referred to as "AF begets AF" (Fig. 1, (88)). AF is associated with rapidly developing shortening of action potential duration (APD) and effective refractory period (ERP). In addition, rate-dependent adaptation of these two parameters is lost in fibrillating atria. These changes that are referred to electrical remodeling develop faster than the tendency for persistence of AF, suggesting that an additional "second factor" as for instance structural changes must take place (80, 88). Indeed, histological alterations after long lasting AF support the existence of structural remodeling (33). The tendency for persistence of AF is explained by electrophysiological and structural adaptation processes called electrical and structural "remodeling". This involves alterations in myocardial electrophysiological and histological properties as well as changes in Ca^{2+} handling of the cells. Understanding the molecular mechanisms underlying atrial remodeling in human atria is necessary to identify targets for new drugs that may eventually improve conversion to and maintenance of SR in patients with chronic AF.

Although a detailed account of structural remodeling is beyond the scope of this article (an excellent review on this topic was recently published by Allessie et al. (5)), we will give a brief survey of the changes involved. Structural

BRC 409

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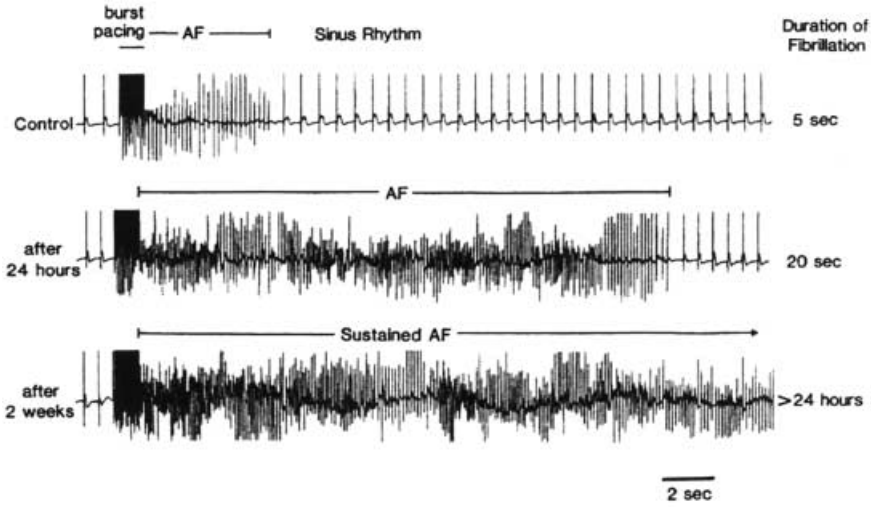

Fig. 1 Duration of AF produced by electrical burst pacing in a chronically instrumented goat after AF had been induced for the durations indicated to the left of each panel (reproduced from ref. (88))

remodeling leads to changes in tissue and myocyte morphology, to interstitial fibrosis and apoptotic cell death (1, 8, 52, 68, 79). In analogy to heart failure, AF is also associated with activation of the atrial angiotensin system leading to progressive atrial fibrosis (37, 38), which is attenuated by ACE inhibition (71). Atrial regions with advanced fibrosis or amyloidosis exhibit slow conduction and can represent local "sources" for AF. In addition, cardiomyocyte hypertrophy, loss of sarcomeres (myolysis) and glycogen accumulation were the major histological findings in atria from patients with lone and chronic AF (33, 68, 92). Similar changes were found in the atria of a goat model of AF (8). In this animal model, the subcellular changes included alterations in mitochondrial shape, fragmentation of sarcoplasmic reticulum, and homogeneous distribution of chromatin which resemble the situation in fetal cardiomyocytes. This suggests that cardiomyocytes dedifferentiation may occur during AF. Collectively, these data indicate that AF is associated with profound changes in tissue and cellular structure which may contribute to stabilization of AF and to reduced efficacy of pharmacologic cardioversion in AF (10).

Several excellent reviews based on clinical and experimental evidence for electrical remodeling in chronic AF have appeared in the past years (3, 5, 60, 61, 83). AF-associated changes in cellular electrophysiology were first analyzed in animal models of rapid atrial pacing (95, 96). However, extrapolation of those findings to humans may be inappropriate because of species differences and undue simplifications. Furthermore, human tissue is usually available from diseased hearts only, where age, underlying heart disease, or concomitant medication may have an additional influence so that pathophysiological processes accompanying human AF may differ from corresponding animal models. Therefore, the present update will be restricted to data from human atrial tissue and, after a brief description of initiation of AF, will focus on cellular electrical remodeling in chronic AF and the time courses of these changes. In addition, the putative molecular mechanisms in electrical remodeling will be considered as possible targets for treatment.

Trigger and reentry

AF is initiated when an abnormal excitation encounters a pathological substrate. Typical triggers for AF are abnormal activity of the sympathetic or parasympathetic nervous system, bradycardia, premature atrial extrasystoles (11) or rapidly firing ectopic foci located in the muscular sleeves of the pulmonary veins (44). Either sympathetic or vagus nerves stimulation reduces the wavelength for reentry (see below) by shortening atrial refractoriness, though conduction velocity is slightly but significantly increased (57). Nevertheless, vagal nerve activation is generally more effective in promoting initiation and persistency of AF than sympathetic stimulation probably due to concomitant bradycardia and parasympathetically increased heterogeneity in atrial refractoriness. The substrate can be produced by abnormal activation of the angiotensin system that produces atrial fibrosis (37, 38, 52), or by the tachycardia itself, which leads to electrical remodeling of the atria. The subsequent AF-related abbreviation of APD and ERP probably increases the vulnerability of AF to premature beats. Shortening in ERP and/or structural adaptations provide the arrhythmogenic substrate that allows reentry of the excitation wavefront and thus sustains the arrhythmia (2). The wavelength for functional reentry is the product of ERP and conduction velocity (2, 65), so that either shortening of ERP and/or reduction of conduction velocity will facilitate reentry and hence augment the likeli-

hood and duration of AF. Accordingly, AF should become sustained, if the "excitable gap" between the excitation front and refractoriness produced by the preceding wavelet is widened by shortening of ERP or slowing of conduction. Atrial fibrillation can be maintained by ectopic foci, by a single- or by a multiple-circuit reentry. Investigating the activation pattern in fibrillating atria with mapping systems reveals that the three primary mechanisms are not independent and promote the occurrence of the one another. Ectopic foci can be the triggers in the induction of a single-circuit reentry and can promote the occurrence of multiple-circuit reentry by inducing tachycardia. On the other hand, a single-circuit reentry can promote the induction of multiple-circuit reentry by causing atrial remodeling.

Electrical remodeling in human chronic AF

Early evidence for electrical remodeling in patients was provided by Attuel et al. (7) who observed that impaired adaptation of APD to changes in cardiac cycle length is associated with increased vulnerability to AF. Since then, electrical remodeling has been demonstrated in several clinical settings (26, 32, 34, 48, 49, 97) and is associated with inhomogeneous shortening of APD and ERP accompanied by enhanced spatial heterogeneity of repolarization and loss of rate adaptation of both repolarization and refractoriness. It is not clear how blunted rate adaptation of APD and ERP can contribute to the promotion and perpetuation of AF. APD and ERP of myocytes from patients in AF vary within much smaller limits because they are already short at regular rates due to electrical remodeling and are not much further abbreviated at high stimulation rates due the blunted rate adaptation. The smaller rate-dependent variation in APD and ERP is expected to enhance homogeneity of repolarization rather than to increase heterogeneity. Provided that heterogeneity of ERP promotes initiation of AF, increased homogeneity should counteract it. At present, this issue has not been resolved.

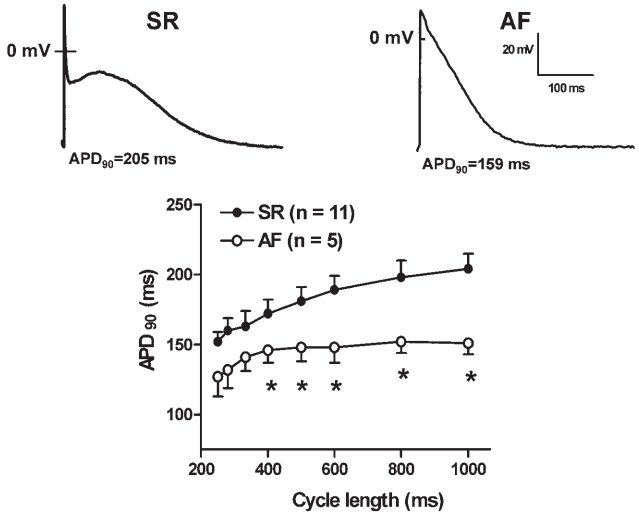

Fig. 2 Top, Representative APs recorded in human right atrial trabeculae from patients in SR (left panel) and in AF (right panel, cycle length 1000 ms. Bottom, Cycle length-dependence of APD_{90} (means ± SEM). *$p < 0.05$ versus SR. Compiled from data published by ref. (28)

Molecular basis for electrical remodeling

Shortening of APD and the loss of rate adaptation are detectable in atrial tissue and also in atrial myocytes from patients in chronic AF (Fig. 2, see also (14)). Since such isolated muscle preparations are cut off from regulation by autonomic nerves, the electrophysiological changes must be due to AF-induced modulation of the ion channels that are responsible for the shape of the cardiac action potential. Generally speaking, electrical remodeling can occur at the level of ion channel expression or by modification of ion channel properties.

The characteristic shape of the human atrial AP is generated by ion fluxes through voltage-dependent ion channels (Fig. 3, (78)). Depolarizing inward Na^+ and L-type Ca^{2+} currents ($I_{Ca,L}$) are balanced by a diversity of repolarizing K^+ outward currents (Fig. 3). Cells with pacemaker activity are depolarized by an inward pacemaker current I_f. In addition, electrogenic carrier and transporter proteins, e.g., the Na^+,K^+-ATPase and the Na^+-Ca^{2+} exchanger, may generate current which in the range of the resting membrane potential, contributes to hyperpolarization or depolarization, respectively (35, 72). The Na^+-Ca^{2+} exchanger utilizes the electrochemical gradient for Na^+ and allows 3 Na^+ to enter for each Ca^{2+} removed. Hence it will contribute net inward (depolarizing) current in the terminal phase of repolarization (see below). The repolarizing K^+ currents include the transient outward current I_{to}, the rapidly activating outward rectifier I_{Kur}, the rapid (I_{Kr}) and the slow (I_{Ks}) delayed rectifiers and the three inward rectifiers, I_{K1}, ACh-activated $I_{K,ACh}$, and ATP-sensitive $I_{K,ATP}$. The AF-related shortening of the APD can be attributed to decreased inward currents, enhanced outward K^+ currents or a combination of both. In search for the mechanisms responsible for APD shortening, numerous voltage-clamp studies have dealt with these ionic currents in SR and chronic AF. Please note that the studies outlined below defined clinical AF as chronic when it was persisting for more than 3 to 6 months and did not differentiate between persistent and permanent AF.

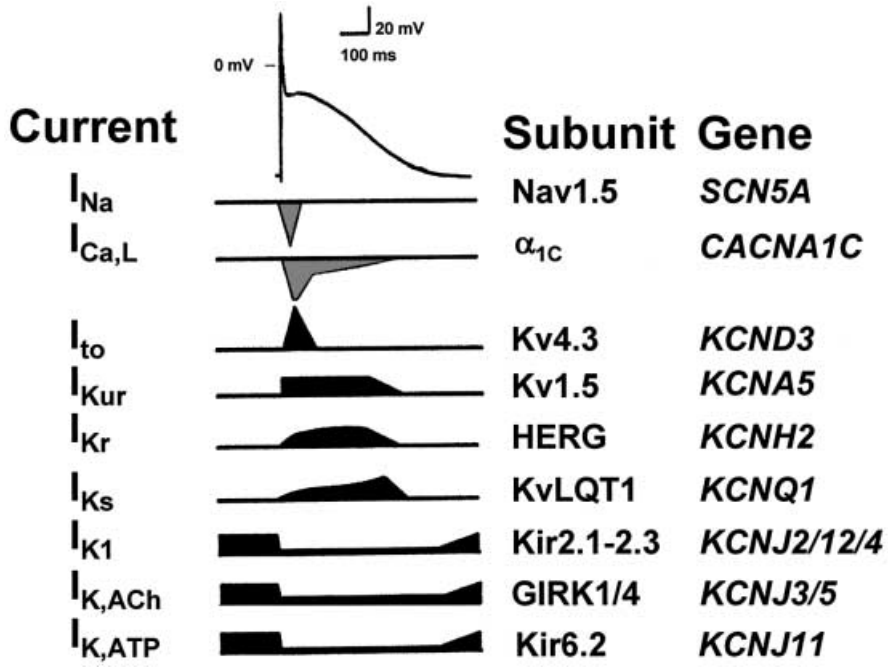

Fig. 3 Ionic currents contributing to the shape of the human atrial action potential. The currents are indicated on the left, the genes encoding the corresponding channel sununits shown on the right. The time course and the directions of the currents are presented in the middle (downward direction indicates depolarising, upward direction repolarizing currents, respectively)

Inward directed ion currents

Since Na^+ current is one major determinant of conduction velocity, modulation by disease or drugs may favor reentry and hence perpetuation of AF. In myocytes from patients in chronic AF, there is no change in Na^+ current density (13) nor in expression of the Na^+-channel α-subunits at the mRNA level (17). Thus, altered Na^+ current activity apparently does not contribute to electrical remodeling in human chronic AF.

The major inward current during the plateau phase, $I_{Ca,L}$, is reduced in amplitude by 70% in patients with chronic AF (Table 1). The reduced current density is accompanied with a decrease in mRNA expression and with an even stronger decrease in protein levels of the pore-forming α_{1C} channel subunit (Table 1). Therefore, the decreased density of $I_{Ca,L}$ is probably due to reduced expression of the respective channel subunits, although this conclusion has been challenged by others who did not find any reduction of α_{1C} subunit expression (43, 70) suggesting that additional mechanisms for current reduction may be involved. Interestingly, exposure of atrial myocytes from SR patients to 10 μM nifedipine to inhibit $I_{Ca,L}$ produces an AP configuration qualitatively similar to that associated with AF (84). Thus, there is strong evidence that down-regulation of $I_{Ca,L}$ may contribute to electrical remodeling in human chronic AF.

Table 1 Expression and activity of L-type Ca^{2+} current ($I_{Ca,L}$) in human chronic AF as compared to SR

References	$I_{Ca,L}$	α_{1C}-Subunit mRNA	α_{1C}-Subunit Protein
Bosch et al., 1999 (13)	–70%	n.d.	n.d.
Lai et al., 1999 (54)	n.d.	–60%	n.d.
Van Gelder et al., 1999 (81)	n.d.	–49%	n.d.
Brundel et al., 1999 (18)	n.d.	–57%	–43%
Van Wagoner et al., 1999 (84)	–63%	n.d.	n.d.
Grammer et al., 2000 (41)	n.d.	–19%	n.d.
Schotten et al., 2000 (70)	n.d.	n.d.	↔
Grammer et al., 2001 (43)	n.d.	↔	n.d.
Skasa et al., 2001 (73)	–72%	n.d.	n.d.
Workman et al., 2001 (91)	–65%	n.d.	n.d.
Brundel et al., 2001 (17)	n.d.	–24%	–56%

n.d. not determined, ↔ = not significantly changed

Unselective cation channels carry the hyperpolarization pacemaker current I_f that could be detected in human atrial myocytes (46). Increased pacemaker current I_f could contribute to atrial ectopic activity. In fact, mRNA of I_f channels is increased in AF compared with SR (56); however, equivalent electrophysiological data has not yet been provided.

During diastole the intracellular Ca^{2+} is removed by uptake into the sarcoplasmic reticulum and by extrusion from the myocytes via transmembrane Na^+-Ca^{2+} exchanger. Due to its electrogenicity (see above), the Na^+-Ca^{2+} exchanger produces a net inward current during Ca^{2+} extrusion which can generate afterdepolarizations (72). The protein expression of the Na^+-Ca^{2+} exchanger is substantially increased in atria from patients with chronic AF (69); however, functional activ-

ity has not been studied. If increased expression of Na^+-Ca^{2+} exchanger is associated with enhanced function, afterdepolarizations and triggered activity are anticipated and could contribute to the persistence of AF.

Conduction of electrical impulses depends on the magnitude of I_{Na} and electrical cell-to-cell coupling which is determined by the special proteins called connexins. At the sites of contact, neighboring myocytes contribute one hemichannel each to form the full ion channel required for cell-to-cell communication (27). Under normal conditions, most connexins are located at the cell poles with very few found in the lateral contact membranes, but more channels are found in the latter location in chronic AF (62). Human chronic AF has also been associated with altered expression of connexin channel proteins, though published data are inconsistent. Several patterns of AF-induced changes in protein expression have been reported with expression of connexin43 unchanged and connexin40 increased (62); expression of both types of connexins reduced (52), and connexin40 increased (patients with postoperative AF, (30) see below). Without further information where the changes are localized within the myocyte, these data are difficult to interpret, because enhanced expression of connexins at the cell ends is expected to improve conduction (and hence terminate AF), whereas preferred lateral expression of connexins should change anisotropy and hence favor reentry.

Table 2 Expression and activity of the transient outward K^+ current (I_{to}) and the rapidly activating outward rectifier K^+ current (I_{Kur}) in human chronic AF as compared to SR

References	I_{to}	Kv4.3-Subunit mRNA	Protein
Van Wagoner et al., 1997 (85)	–66 %	n.d.	n.d.
Bosch et al., 1999 (13)	–70%	n.d.	n.d.
Brandt et al., 2000 (15)	–44%	n.d.	n.d.
Grammer et al., 2000 (42)	n.d.	–61%	n.d.
Brundel et al., 2001 (17)	n.d.	–22%	–49%
Brundel et al., 2001 (19)	n.d.	–35%	–39%
Workman et al., 2001 (91)	–65%	n.d.	n.d.
References	**I_{Kur}**	**Kv1.5-Subunit mRNA**	**Protein**
Van Wagoner et al., 1997 (85)	–49 %	n.d.	–54%
Lai et al., 1999 (55)	n.d.	–30%	n.d.
Bosch et al., 1999 (13)	↔	n.d.	n.d.
Brandt et al., 2000 (15)	–55%	n.d.	n.d.
Grammer et al., 2000 (42)	↔	↔	n.d.
Brundel et al., 2001 (17)	n.d.	↔	–54%
Brundel et al., 2001 (19)	n.d.	↔	–84%
Workman et al., 2001 (91)	↔	n.d.	n.d.

n.d. not determined, ↔ = not significantly changed

Outward rectifier potassium currents

The early repolarization phase is dominated by the rapidly activating outward currents I_{to} and I_{Kur} and sets the potential for activation of plateau currents mainly $I_{Ca,L}$. Chronic AF is associated with strong reduction of I_{to} density (Table 2) and with diminished expression of the respective channel subunits (Table 2). There is also evidence for decreased I_{Kur} density and expression of its channel subunits (Table 2). However, the reduction of I_{Kur} may occur only in a subpopulation of patients with chronic AF, because it could not be confirmed by others (Table 2). In any case, the reductions of I_{to} and I_{Kur} were unexpected, since reduced densities of outward currents prolong APD and ERP, whereas the opposite is found in AF. Therefore, it is unclear how decreased current density of I_{to} and I_{Kur} could contribute to electrical remodeling in chronic AF.

Changes in activity of the rapid and slow delayed rectifiers I_{Kr} and I_{Ks} may also be involved in AF-induced electrical remodeling. However, up to now there are no electrophysiological data from human atrium and expression of the respective channel subunits provided contradictory results with decreased (19, 55) or no change in expression of I_{Kr}-encoding HERG mRNA (17), and decreased (55) or increased expression of I_{Ks} transcripts ((19), see also Table 3).

Inward rectifier potassium currents

The inward rectifier I_{K1} is responsible for maintenance of the stable, strongly negative resting membrane potential and augments repolarization during the late phase of the AP (47). Under physiological conditions this highly selective K^+ channel passes repolarizing outward current. I_{K1} density is larger in myocytes from patients with

Table 3 Expression of the rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifiers in human chronic AF as compared to SR

References	I_{Kr}	HERG-Subunit mRNA	Protein
Lai et al., 1999 (55)	n.d.	–27%	n.d.
Brundel et al., 2001 (17)	n.d.	–22%*	–34%
Brundel et al., 2001 (19)	n.d.	↔	n.d.
References	**I_{Ks}**	**K_vLQT1-Subunit mRNA**	**Protein**
Lai et al., 1999 (55)	n.d.	–30%	n.d.
Brundel et al., 2001 (17)	n.d.	+56%	n.d.

* Only by patients with chronic AF and mitral valve disease, but not by those with lone AF

n.d. not determined, ↔ = not significantly changes

Table 4 Expression and activity of the inward rectifiers I_{K1} and $I_{K,ACh}$ in human chronic AF as compared to SR

References	I_{K1}	Kir2.1-Subunit mRNA	Kir2.1-Subunit Protein
Van Wagoner et al., 1997 (85)	+106%	n.d.	n.d.
Bosch et al., 1999 (13)	+100%	n.d.	n.d.
Dobrev et al., 2001 (28)	+137%	+141%	n.d.
Dobrev et al., 2002 (29)	+ 73%	n.d.	n.d.
Workman et al., 2001 (91)	+ 75%	n.d.	n.d.
References	**$I_{K,ACh}$**	**GIRK1/GIRK4-Subunit mRNA (GIRK4)**	**GIRK1/GIRK4-Subunit Protein (GIRK1)**
Bosch et al., 1999 (13)	+45%	n.d.	n.d.
Dobrev et al., 2001 (28)	–47%	–32%	n.d.
Brundel et al., 2001 (17)	n.d.	–31%	–52%
Brundel et al., 2001 (19)	n.d.	–47%	–47%
Dobrev et al., 2002 (29)	–54%	n.d.	n.d.

n.d. not determined

chronic AF than with SR (Table 4). There is good quantitative agreement between increased I_{K1} and the extent of up-regulation of the main I_{K1} transcript Kir2.1 (28). I_{K1} is the only K^+ outward current which shows increased and not decreased density in human chronic AF. In correspondence to the *increased* density of I_{K1}, the resting membrane potential was more negative in myocytes or trabeculae from AF than from SR patients (28, 29).

The clinical impact of increased I_{K1} is currently not clear; however, in our view, the changes appear to be adaptive mechanisms (see below). This is supported by the hypothesis that intrinsic pacemaker activity of atrial and ventricular adult myocytes is suppressed by I_{K1} (58, see also 98). These authors succeeded to unmask pacemaker activity in guinea-pig ventricular myocytes by genetically engineering a dominant-negative mutant of the Kir2.1 protein that in combination with the wildtype subunit dramatically reduced I_{K1} current density. Ventricular cells containing the mutant generate spontaneous, rhythmic electrical activity (Fig. 4). Thus, the increased density of I_{K1} in chronic AF may serve as a compensatory mechanism against the increased electrical activity of the fibrillating atria.

However, for ventricular fibrillation it was reported that decrease in rectification of I_{K1} resulted in stable and high frequency rotors that stabilize reentry (66). If a similar pathomechanism is also involved in chronic AF, larger current in the outward branch (or shorter APs) could contribute to maintenance of AF. These two opposing interpretations cannot be resolved at present.

Changes in the autonomic nervous system are important for initiation and perpetuation of AF. Sympathetic activation appears to be involved in the induction of postoperative AF (84). Vagal stimulation or acetylcholine application also induce AF (4, 21, 23, 57). Vagal stimulation shortens atrial APD and ERP, increases atrial conduction velocity and promotes reentry (4, 6, 51, 57, 63). These effects are mediated by $I_{K,ACh}$, the major effector of cholinergic stimulation in the heart (93), because in knock-out mice lacking this channel, muscarinic receptor stimulation did not induce AF (53). Thus, increased activity of $I_{K,ACh}$ could explain AF-related shortening of APD. Accordingly, one recent study demonstrated increased activity of $I_{K,ACh}$ in atrial myocytes from patients with chronic AF (13). In atrial biopsies from patients with AF, activity of acetylcholine esterase is significantly reduced (40), hence endogenously released ACh is expected to have an enhanced and prolonged action. However, in our hands the response of $I_{K,ACh}$ to muscarinic receptor activation is *smaller* in AF than in SR and is in line with reduced channel expression in chronic AF (Table 4). In addition we found that shortening in

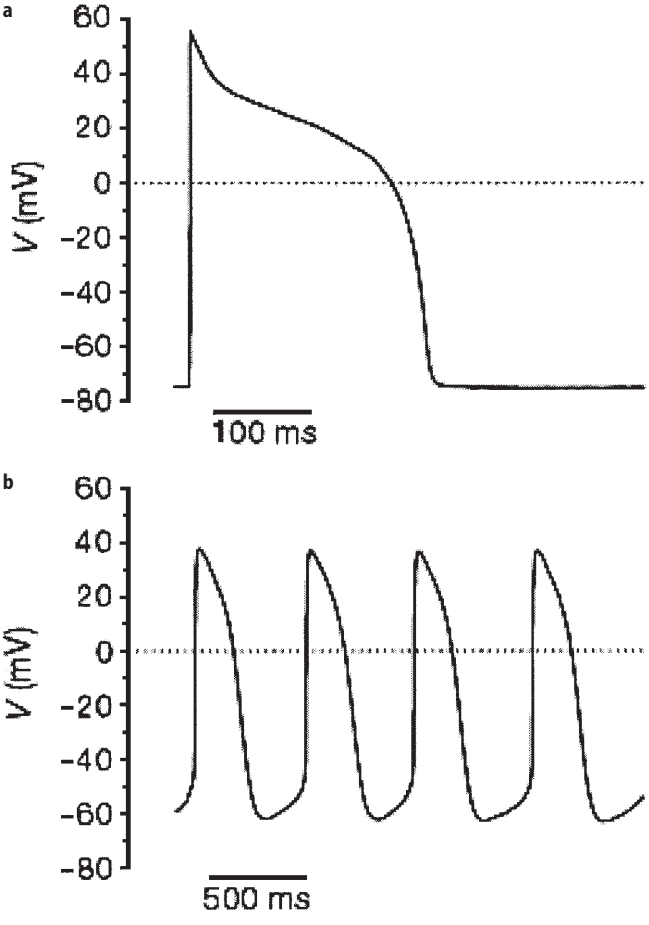

Fig. 4 Unmasking pacemaker activity in guinea-pig ventricular cells by genetically engineering a dominant negative mutant of the Kir2.1 channels. **a** Stable action potentials evoked by depolarizing external stimuli in control ventricular myocytes. **b** Myocytes containing the mutant generate spontaneous, rhythmic electrial activity (reproduced from ref. (58))

APD by muscarinic receptor stimulation is smaller in AF than in SR, corresponding to the reduction of $I_{K,ACh}$ current density and channel expression. Thus, atrial myocytes probably adapt to a high beating rate by downregulating $I_{K,ACh}$ to counteract the shortening of APD (28).

The ATP-sensitive K^+ current is a weak inward rectifier that activates upon a drop in intracellular ATP concentration. Although activated $I_{K,ATP}$ could strongly abbreviate atrial APD its function in AF has not been investigated. The only published data showed a decrease in expression of Kir6.2 mRNA (19); the functional significance of this finding is not known.

In conclusion, there is strong evidence for altered ion channel activity associated with human chronic AF. In this setting, reduced density of $I_{Ca,L}$ and increased activity of I_{K1} may be the main ionic determinants of electrical remodeling. However, whether these current changes are cause or consequence of AF has still to be established.

Time course of electrical remodeling

Characterization of the time courses of the above described changes is essential for discrimination between cause and consequence in chronic AF. This differentiation is a prerequisite for selecting appropriate targets for therapeutic intervention. Investigation of the time course of electrical remodeling at a cellular level is, however, not feasible in a clinical setting.

Clinically, episodes of AF reduce APD and ERP within a few minutes (75, 76) which results from functional changes in activity of ion currents and does not involve modified gene expression of the corresponding channels. In contrast, rapid atrial pacing in animal models decreases the refractoriness gradually with a time course of several hours, reaching a maximum usually within 2 – 7 days (36, 89). Thus, the gradual changes in refractoriness by rapid pacing for several hours and days might result from alterations in the gene expression of ion channels. Data from a rat model of pacing-induced atrial tachycardia suggest that the alterations in I_{to} and I_{Kur} channel expression start after several hours of atrial pacing (94). Current density of $I_{Ca,L}$ and expression of the respective channel subunits were substantially reduced after 6 to 24 hours of rapid atrial pacing (rabbit, 12; dog, 95, 96).

Within the first minutes of AF, metabolic adaptations occur which are paralleled by an increase in oxygen consumption and coronary flow, a reduction in atrial creatine phosphate and probably by oxidative stress (9, 20, 87). The metabolic changes are associated with an increase of the intracellular Ca^{2+} concentration (Ca^{2+}-overload), which results in rapid inactivation of $I_{Ca,L}$ and shortening of the APD. During the first week of AF, a further gradual decrease in APD and ERP occurs, thereafter, reaching a new steady-state level. This stage involves altered expression of a variety of ion channels (95, 96) and cannot be explained by metabolic changes only. Finally, AF lasting for several months or years is chararterized by progressive structural remodeling (see above). The latter plays an important role in the stabilization of AF. Although clinical AF decreases APD and ERP with a time scale of minutes (75, 76), the underlying molecular mechanisms are not fully understood.

If atrial remodeling plays a major role for postoperative AF, this condition may indirectly allow discrimination between cause and consequence of ion channel alterations. In the case of ion channel changes triggering AF, we would expect to detect altered current density as an indicator of these changes already *before* the onset of the arrhythmia. In contrast, if ion channel changes occur as a consequence of AF, no current changes are expected in myocytes from tissue sampled at the time of cardiac surgery when the patient is still in SR. Density of $I_{Ca,L}$ is increased in myocytes from patients who are in SR at the time of heart surgery but develop AF in the postoperative period in comparison to patients without postoperative AF (84). This indicates that increased Ca^{2+} influx may contribute to the initiation of AF, whereas the reduced density of $I_{Ca,L}$ during chronic AF may be a compensatory mechanism to limit Ca^{2+} influx into the fibrillating atria. Density of I_{to} and I_{Kur} does not differ between patients who maintain SR and those who develop postoperative AF suggesting that involvement of these currents in the initiation of AF is rather unlikely (15) and that other mechanisms must be involved.

Since parasympathetic stimulation and the subsequent activation of $I_{K,ACh}$ can induce AF (4, 6, 21, 23, 57), increased $I_{K,ACh}$ density could initiate postoperative AF. However, current amplitudes of I_{K1} and $I_{K,ACh}$ do not differ in SR patients with and without postoperative AF suggesting that the AF-related changes of I_{K1} and $I_{K,ACh}$ are most likely a *consequence* of AF (29).

Putative molecular mechanisms of electrical remodeling

As mentioned in the previous section, alterations in ion channel activity appear to be mainly mediated by modified transcription of respective ion channel subunits. If the expression of channel protein is controlled only by the rate of transcription of mRNA, protein levels and mRNA should change in parallel. However, in chronic AF, this is not always true with large discrepancies in expression of mRNA and proteins in some cases. For $I_{Ca,L}$ and I_{to}, expression of mRNA and protein are reduced in parallel (see Tables 1 and 2), whereas for I_{Kur}, expression of Kv1.5 mRNA is not, but protein is reduced by about 65 % (Table 2). Alterations in I_{Kr} and the changes in

expression depend on the type of AF, i.e., whether it is lone AF or AF with mitral valve disease (Table 3). Taken together, the discrepancies between mRNA and their respective channel proteins suggest that in addition to transcription rate, different translational efficiencies, posttranslational modifications and/or degradation processes (proteolysis) control ion channel expression in electrical remodeling (16, 39, 59).

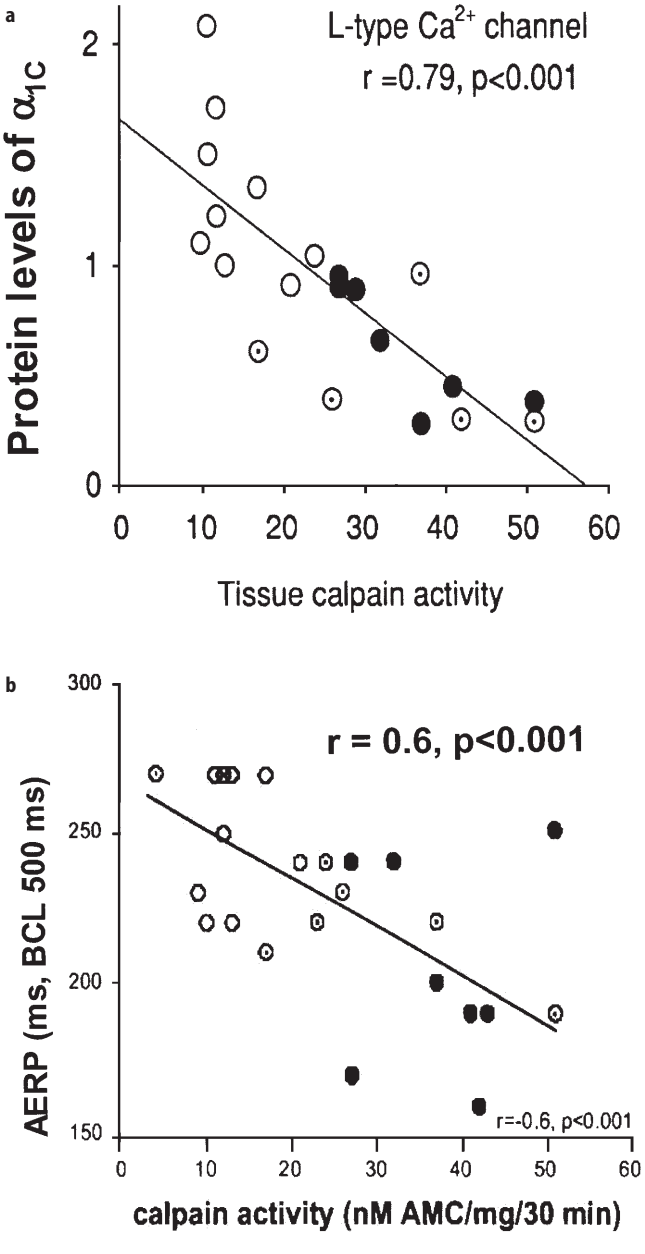

Fig. 5 Correlation between tissue calpain activity and expression of L-type Ca^{2+} channels (**a**) and duration of atrial effective refractory period (AERP, **b**). ○ indicates patients with SR, ⦿ with paroxysmal AF, and ● with chronic AF, respectively (reproduced from ref. (16))

The primary stimulus for AF-induced electrical remodeling is the dramatic increase in atrial rate. With every AP, Ca^{2+} ions enter the cell via L-type Ca^{2+} channels and cannot be sufficiently removed from the cytosol because of the extremely short diastolic intervals (50, 77). Direct evidence for Ca^{2+} overload is obtained from in vitro experiments with canine atrial myocytes, where abrupt increases in frequency from 0.3 to 3 Hz cause rapid increases in diastolic Ca^{2+} levels (77). Indirect evidence for an increased Ca^{2+} loading during human chronic AF is provided by the increase in glucose-regulated protein 94 (GRP94) in the respective atrial tissue (86). GRP94 is a low-affinity high-capacity Ca^{2+}-binding protein that is expressed in the sarcoplasmic reticulum where it protects the cells against stress due to Ca^{2+} depletion from sarcoplasmic reticulum (25). Oxidative products cause Ca^{2+}-overload of cardiac myocytes and oxidative stress appears to be involved in the pathogenesis of human AF, since ascorbic acid reduces the incidence of postoperative AF (20). In addition, chronic AF enhances activity of calpains (16, 39). These Ca^{2+}-activated neutral proteases cleave mainly cytoskeletal and membrane-bound proteins (74). Increased cellular Ca^{2+} levels activate calpains by autocleavage leading to increased proteolytic activity and simultaneously, to enhanced Ca^{2+} sensitivity of the enzyme. Interestingly, Brundel and coworkers found a significant inverse correlation between calpain activity in atrial tissue and the protein levels of L-type Ca^{2+} and several K^+ channels (16). Tissue calpain activity also correlated with the duration of atrial ERP suggesting that increased proteolytic activity may play an important role in electrical remodeling (Fig. 5). Though direct proof of a causal relationship between calpain activity and reduction of channel protein expression is still pending, the hypothesis is attractive because it links increased Ca^{2+} influx during AF initiation to the molecular changes observed in this arrhythmia.

Ion channels as drug targets for treatment of chronic AF

The pathophysiological concept of triggers and perpetuators of AF points towards three major targets for pharmacological intervention, i.e., excitability, conduction velocity and ERP. In the above sections we have outlined the numerous changes in ion channel activity and expression that occur during electrical remodeling. Since the latter is related to the tendency of chronic AF to become persistent and permanent, the question arises whether reversal of AF-induced changes in ion channel activity may represent a therapeutic option for long-term conversion to SR.

Excitability of cardiac cells is a function of I_{Na} and I_{K1} activity; its effective suppression requires decreased I_{Na}

and/or enhanced I_{K1}. However, reduced I_{Na} also impairs conduction velocity and promotes occurrence of reentry. Therefore this mechanism is not expected to translate into a therapeutic benefit. On the other hand, I_{K1} is already increased in response to the high rate of electrical activity in AF and the outcome of further augmentation is dificult to predict because it will stabilize the membrane potential but reduce ERP and hence enlarge the excitable gap (see below).

Interruption of reentry circuits can be interrupted by enhancing conduction velocity, or by complete conduction block. The cellular targets are Na^+ channels and various connexins. No drugs are available for enhancing peak I_{Na} amplitude and suppression of conductance is accompanied by severe pro-arrhythmic effects also in the ventricles (31). Nevertheless, in chronic AF it was recently shown that for instance the class I antiarrhythmic drug flecainide did not prolong wavelength but instead widened the excitable gap immediately prior to successful drug-induced conversion to SR (90). Connexins are attractive targets, which despite the present lack of modulating drugs, could become subject to manipulations by suitable genetic approaches in the future.

Since the short APs in chronic AF are associated with altered ion channel activity, one would expect to normalize APD and ERP by restoring ion channel activity. However, increasing the reduced $I_{Ca,L}$ may be pro-arrhythmic because Ca^{2+} channel openers can prolong APD producing early afterdepolarizations. On the other hand, most patients with chronic AF could tolerate the prolongation of APD if cardioversion of the arrhythmia can be achieved. With exception of I_{K1}, the repolarizing K^+ currents are reduced in activity; therefore further blockade may not provide sufficient prolongation of ERP to terminate AF. Although block of increased I_{K1} activity appears an intriguing option, reduction of this current may be proarrhythmic due to increased pacemaker activity in the atria and ventricles (58).

Autonomic nervous system modulates the AP configuration by altering ion channel activity (57, 64). Enhanced sympathetic drive increases $I_{Ca,L}$ providing the molecular substrate for early afterdepolarization. However the maximum current density of $I_{Ca,L}$ in response to catecholamines is smaller in chronic AF than in SR (84). Thus further reduction by pharmacological block of $I_{Ca,L}$ could counteract the effects of elevated sympathetic activity. Catheter ablation of cardiac parasympathetic nerves in dogs prevents vagal atrial fibrillation (67), suggesting that at least in some patients with AF the inhibition of the parasympathetic nervous system may have an antiarrhythmic effect. The main effector of vagal activation is $I_{K,ACh}$; the density of which is reduced in chronic AF (28, 29). Although discussed as a new principle for rate control in AF (99), a therapeutic increase in $I_{K,ACh}$ activity does not appear beneficial, because parasympathetic activation may induce AF (see above).

Since pulmonary veins represent a common source for ectopic foci, their electrophysiological characteristic may lend themselves as targets for drug threatment. Stable action potentials were found in the muscular sleeves near the ostium and automaticity was absent when the pulmonary veins were electrically coupled to the atria (45). Ectopic beats from pulmonary veins were suppressed by β-adrenoceptor blockers, calcium channel blockers and sodium channel blockers (22).

In conclusion, chronic AF is associated with altered activity of numerous ion channels that are mainly downregulated. Restoring the activity of a single channel species may not be a sufficient therapeutic strategy to reverse electrical remodeling. Furthermore, such options appear to be even harmful when keeping in mind that the AF-induced changes in electrical activity may represent compensatory mechanisms.

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