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Review

Electrical, contractile and structural remodeling during atrial fibrillation

Maurits Allessie*, Jannie Ausma, Ulrich Schotten

Department of Physiology, Cardiovascular Research Institute Maastricht, University of Maastricht, P.O. Box 616, 6200 MD Maastricht, The Netherlands

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Abstract

The natural history of atrial fibrillation (AF) is characterized by a gradual worsening with time. The recent finding that AF itself produces changes in atrial function and structure has provided a possible explanation for the progressive nature of this arrhythmia. Electrical remodeling (shortening of atrial refractoriness) develops within the first days of AF and contributes to an increase in stability of AF. However, 'domestication of AF' must also depend on a 'second factor' since the persistence of AF continues to increase after electrical remodeling has been completed. Atrial contractile remodeling (loss of contractility) leads to a reduced atrial transport function after cardioversion of AF. An important clinical consequence is that during several days after restoration of sinus rhythm, the risk of atrial thrombus formation is still high. In addition, the reduction of atrial contractility during AF may enhance atrial dilatation which may add to the persistence of AF. Tachycardia-induced structural remodeling takes place in a different time domain (weeks to months). Myolysis probably contributes to the loss of atrial contractile force. Although it might explain the loss of efficacy of pharmacological cardioversion and the development of permanent AF, the role of structural remodeling in the progression of AF is still unclear. Atrial structural remodeling also occurs as a result of heart failure and other underlying cardiovascular diseases. The associated atrial fibrosis might explain intra-atrial conduction disturbances and the susceptibility for AF. Thus, both AF itself and the underlying heart disease are responsible for the development of the arrhythmogenic substrate. New strategies for prevention and termination of AF should be build on our knowledge of the mechanisms and time course of AF-induced atrial remodeling.

Keywords: Remodeling; Supraventr. arrhythmia

1. Electrical remodeling

The concept of tachycardia-induced electrical remodeling of the atria was introduced in 1995 by two independent experimental studies [1,2]. In a dog model of prolonged rapid atrial pacing (400/min) Morillo et al. found that the atrial refractory period was reduced by about 15%. In the goat, Wijffels et al. maintained AF by a fibrillation pacemaker automatically delivering bursts of stimuli (1 s, 50 Hz) as soon as sinus rhythm occurred. This resulted in an even more marked shortening in atrial refractoriness from 146±19 to 81±22 ms (−45%) and a loss (or even inversion) of the normal rate adaptation of the refractory period. Given its long-term nature (days to weeks) these tachycardia-induced changes in atrial refractoriness were thought to be due to alterations in the expression of ion channels and were referred to as 'electrical remodeling' [1]. More importantly, these studies showed that long-term rapid atrial pacing or maintenance of AF led to a progressive increase in the susceptibility to atrial fibrillation (AF). After 6 weeks of rapid atrial pacing, in 82% of the dogs episodes of AF lasting >15 min could be induced [2]. In the goat this effect was even more striking. Whereas during control, only short paroxysms of AF were induced by burst pacing (mean 6±3 s), after 2 days of AF the paroxysms lasted more than 4 h (241±459 min) and by that time in two of 12 animals AF had become sustained (>24 h). After 2–3 weeks in 90% of the goats AF was persistent

*Corresponding author. Tel.: +31-43-388-1202/00; fax: +31-43-388-4166.

E-mail address: m.allessie@fys.unimaas.nl (M. Allessie).

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(Fig. 1). This observation of tachycardia-induced electrical remodeling creating a substrate for persistent AF, led to the concept that '*Atrial Fibrillation Begets Atrial Fibrillation*' [1].

The higher susceptibility to AF was explained by a shortening of the wavelength of the atrial impulse [3,4]. When the wavelength is short, small regions of intra-atrial conduction block may already serve as a site for initiation of reentry, thus increasing the vulnerability for AF. A short wavelength is also expected to increase the stability of AF because it allows more reentering wavelets to coexist in the available surface area of the atria. This is illustrated in the right part of Fig. 1, showing high density maps (diameter 4 cm, 240 electrodes) from the free wall of the right atrium during paroxysmal (top) and persistent AF (bottom) [5]. Whereas during control (no remodeling) the right atrium was activated by broad fibrillation waves (type I AF), after electrical remodeling the fibrillation waves were much more disorganized (type III AF) [6]. These different types of AF were first distinguished by Wells et al. [7] based on difference in morphology of bipolar fibrillation electrograms and later by Konings et al. by different degrees of complexities in high density maps of AF [8]. Due to the shortening in wavelength, now multiple wavelets were wandering under the mapping electrode (type III AF). This higher degree of spatial dissociation lowers the chance that the fibrillation waves will all die out, making it less likely that AF will self-terminate.

Shortly after the demonstration of tachycardia-induced electrical remodeling, the ionic mechanisms underlying this arrhythmogenic process have been elucidated by a number of elegant and convincing studies [9–13]. Action potential recordings and patch clamp experiments in isolated atrial cells from animal models and patients in chronic AF showed a consistent pattern. The most important impact of AF on the ion channels was a marked reduction in the L-type Ca^{2+} current. This explains the shortening of the atrial action potential and the loss of the

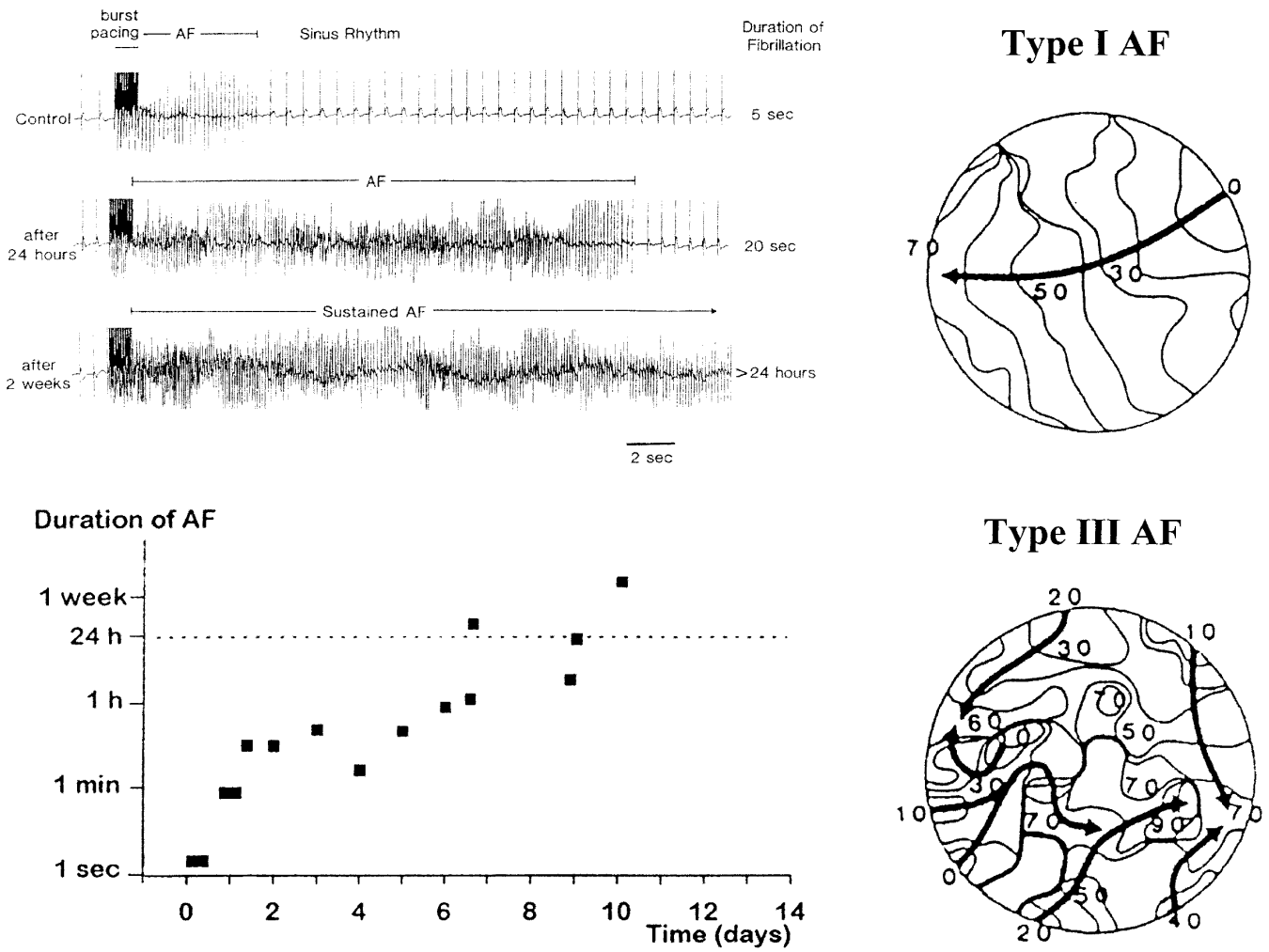


Fig. 1. Left: prolongation of the duration of episodes of electrically induced AF in the goat as a result of electrical remodeling (from Wijffels et al. [1]). Right: high density mapping of the free wall of the right atrium of a goat during acutely induced (top) and persistent AF (bottom). The mapping array (diameter 4 cm) contained 240 electrodes with an interelectrode distance of 2.25 mm. Isochrones are drawn every 10 ms. The direction of propagation is indicated by arrows (from Konings et al. [5]).

physiological rate adaptation of the duration of the action potential [10]. Unexpectedly, also the transient outward current (I_{to}) and the sustained component of the ultra-rapid delayed rectifier ($I_{k,sus}$) were reduced [10,12]. In another study in patients with chronic AF downregulation of $I_{k,sus}$ was not found [14]. Pharmacological probes by which a reduction in I_{Ca} and I_{to} can be mimicked showed that in atrial myocardium I_{to} is of much less importance for the duration of the action potential than I_{Ca} [10]. In Fig. 2 the cellular mechanisms of tachycardia-induced electrical remodeling are summarized. The upper panels show the characteristics of changes in refractory period and action potential in the goat model of AF [1,15]. Already during the first 24 h a dramatic shortening and loss of rate adaptation of the refractory period occurred (A). The complete time course of electrical remodeling of the atrial refractory period is plotted in (B). It took place during the first days of AF and the refractory period reached a new steady state after about 2–3 days. Monophasic action potentials recorded from the free wall of the right atrium before and after chronic AF also clearly demonstrated a shortening of the atrial action potential (inset, B). The two lower panels show the changes in atrial action potentials and L-type Ca^{2+} currents in the dog [10]. During 42 days of rapid atrial pacing a progressive reduction in inward I_{Ca} occurred (C). The voltage, time and frequency characteristics of the L-type Ca^{2+} current remained unchanged. Administration of nifedipine (10 μM) to atrial cells from

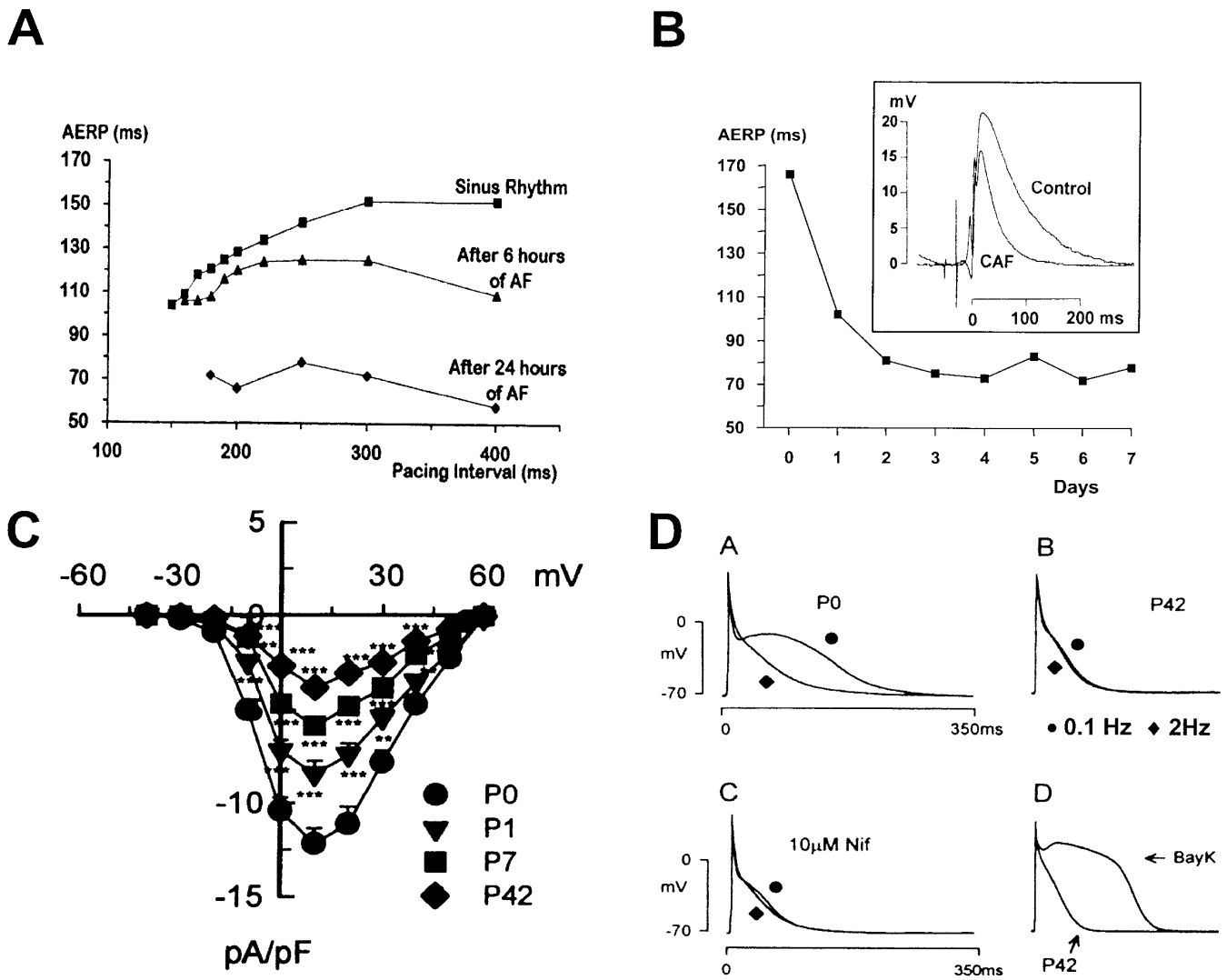


Fig. 2. (A) Shortening of the atrial effective refractory period (AERP) and loss of rate adaptation during 24 h of AF in the goat. (B) Time course of shortening of the AERP by AF (pacing interval 400 ms) (from Wijffels et al. [1]). In the inset monophasic action potentials are superimposed recorded from the free wall of the right atrium during control and after cardioversion of chronic AF (CAF). Note that the duration of the MAP is reduced by about 50% (from Van der Velden et al. [15]). (C) Voltage–current relationships of I_{Ca} during control (P0) and after 1, 7 and 42 days of rapid atrial pacing in the dog. The density of I_{Ca} was progressively reduced with the duration of rapid pacing. (D) Action potentials recorded at 0.1 (●) and 2 Hz (♦) in control atrial cells (P0) and after 42 days of rapid atrial pacing (P42). Addition of nifedipine (C) mimicked the effects of electrical remodeling, whereas the Ca-agonist BayK 8644 restored the plateau phase of the action potential (D) (from Yue et al. [10]).

animals in sinus rhythm mimicked the shortening and loss of rate adaptation due to rapid pacing. Vice versa, adding the Ca^{2+}-channel agonist BayK to a large extent could 'undo' the effects of electrical remodeling (D).

Some important steps in our knowledge of AF-induced electrical remodeling in *humans* are depicted in Fig. 3. The earliest clinical observations that abnormalities in rate adaptation of the refractory period were related to AF were made by Attuel et al. [16]. In 1982 they measured the atrial refractory period in 39 patients and noticed that atrial tachyarrhythmias preferentially occurred in patients in whom the atrial refractory period failed to adapt to changes in pacing rate (Fig. 3A). They suggested that a poor or absent rate adaptation of the atrial refractory period was a marker of some 'cryptic' atrial pathology which caused AF. They further suggested that maladaptation of the atrial refractory period and a propensity to AF together 'constituted a clinical entity' [16]. In 1986, loss of rate adaptation of the refractory period and action potential duration was confirmed in isolated right atrial tissue of patients with chronic AF [17]. The first clinical study demonstrating electrical remodeling in human atria after prolonged tachyarrhythmias was done by Franz et al. [18]. In control patients, the APD_{90} of the monophasic action potential of the right atrium was compared with the APD_{90} in patients with chronic atrial flutter or fibrillation. In patients with AF or atrial flutter, the APD_{90} measured during slow pacing 15–30 min after electrical cardioversion was 130–150 ms shorter than in the control group. The curve describing the relation between the APD_{90} and the steady state cycle length was shifted downward and flattened in the range between 400 and 800 ms (Fig. 3B). In humans the adaptation of atrial refractoriness and APD duration to changes in heart rate is more pronounced than in dog and

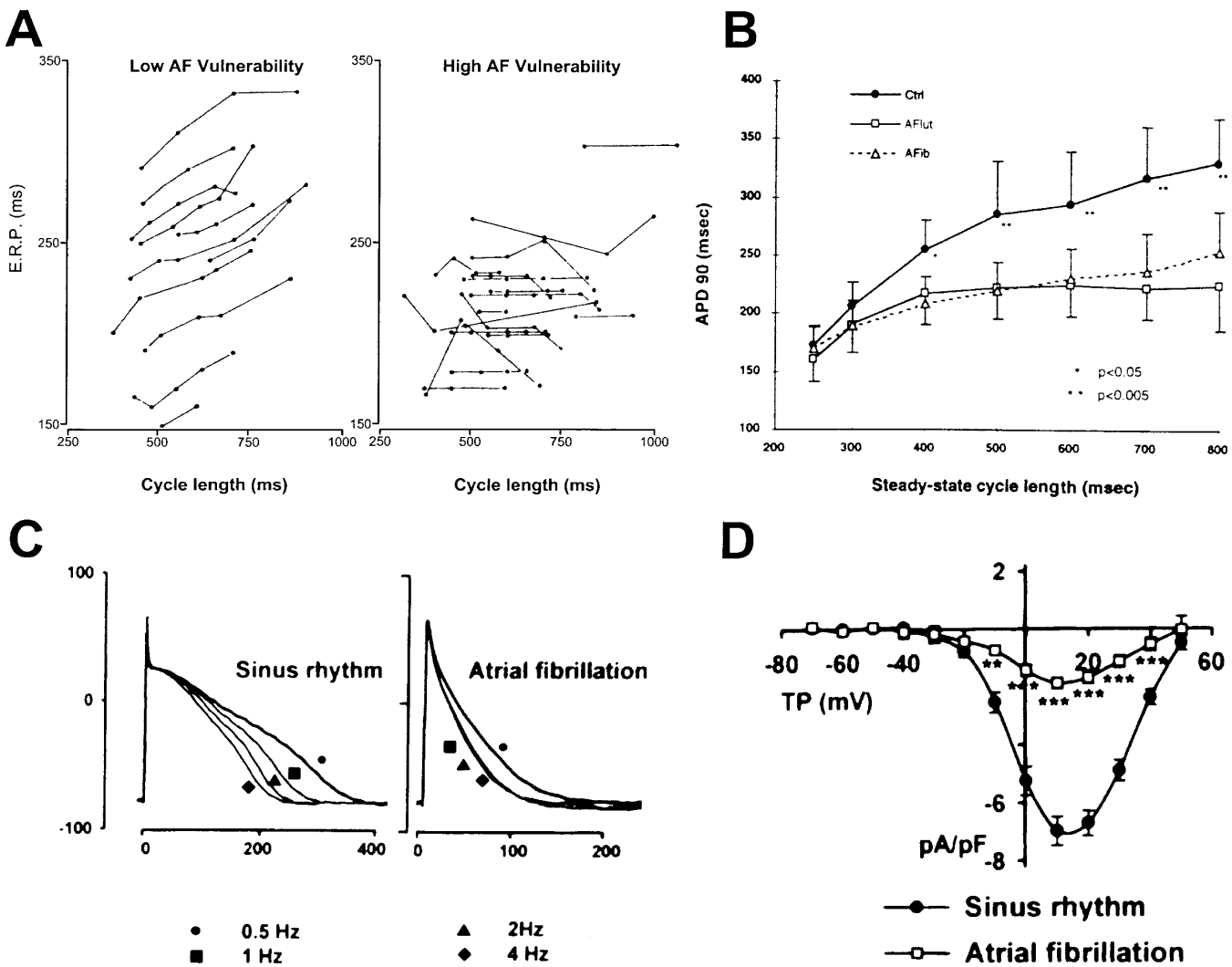


Fig. 3. (A) Physiological rate adaptation of the effective refractory period in 11 control patients (left) and non-adaptation of the ERP in 17 patients with a high vulnerability for atrial fibrillation (right) (from Attuel et al. [16]). (B) Average APD90 duration±S.D. plotted as a function of steady state cycle length. Asterisks denote significant differences in average APD90 of patients with atrial fibrillation (Afib) or flutter (Aflut) (from Franz et al. [18]). (C,D) Action potentials and L-type Ca^{2+} current in atrial cells from humans in sinus rhythm and atrial fibrillation (from Bosch et al. [12].

goat [1,19]. Also the degree of loss of rate adaptation might be different in different patient populations [16,18]. This might explain why in electrically remodeled human atria still some rate adaptation exists at high pacing rates [18]. The association between a short monophasic action potential and the difficulty to maintain sinus rhythm in patients had already been noted earlier by Olsson and co-workers [20,21].

Also on a cellular level the changes in repolarization and ionic mechanisms have shown to be similar as in animal models [11–13,22]. Human AF was associated with a marked shortening in action potential duration and blunting of its rate adaptation (Fig. 3C). As in animal studies, both the transient outward current and the L-type Ca^{2+} current were reduced by about 70% (Fig. 3D). In addition, the recovery from inactivation of the $I_{Ca,L}$ current was slower in cells from AF patients, which contributes to a decreased Ca^{2+} influx at high rates [12]. Van Wagoner et al. showed that, like in the dog model of rapid atrial pacing, the loss of rate adaptation of the action potential could be mimicked by administration of 10 μM of nifedipine [13]. The question whether the reduction in Ca^{2+} influx is solely the result of a reduction of the ion-channel proteins in the cell membrane is not completely settled. In animal models of AF or rapid atrial pacing the mRNA-level of the α_{1C}-subunit of the L-type Ca^{2+} channel was reduced [15,23]. A reduced mRNA content of the α_{1C}-subunit in humans with AF was found in some studies [24,25] but were not confirmed in others [26]. On the protein level, the expression of the α_{1C}-subunit was found to be reduced in one study [25] but not in another [27].

The time course of reverse electrical remodeling after restoration of sinus rhythm has been studied both in goats and humans [1,28]. Even after prolonged periods of AF (months to years), the shortening of the atrial refractory period and diminished rate adaptation are still completely reversible (Fig. 4). The fact that atrial refractoriness becomes normal again within only a few days of sinus rhythm has important clinical implications. It means that recurrences of AF occurring more than 1 week after cardioversion, *cannot* be explained on the basis of abnormalities in atrial repolarization due to electrical remodeling.

It is not yet clear whether prolonged rapid atrial rates also lead to slowing in atrial conduction. Whereas in the dog, after 42 days of rapid pacing a decrease in atrial conduction velocity of 25% was reported [19], mapping of the right atrium in the goat showed no slowing in atrial conduction even after several months of AF [1,15]. At all voltage ranges I_{Na} was significantly reduced in the chronic dog model of AF and its inactivation kinetics were slowed [9]. In contrast, in isolated cells from fibrillating human atria neither the current density nor the voltage dependence of the rapid sodium channels were altered [12]. The voltage-dependent inactivation of I_{Na} was shifted to more

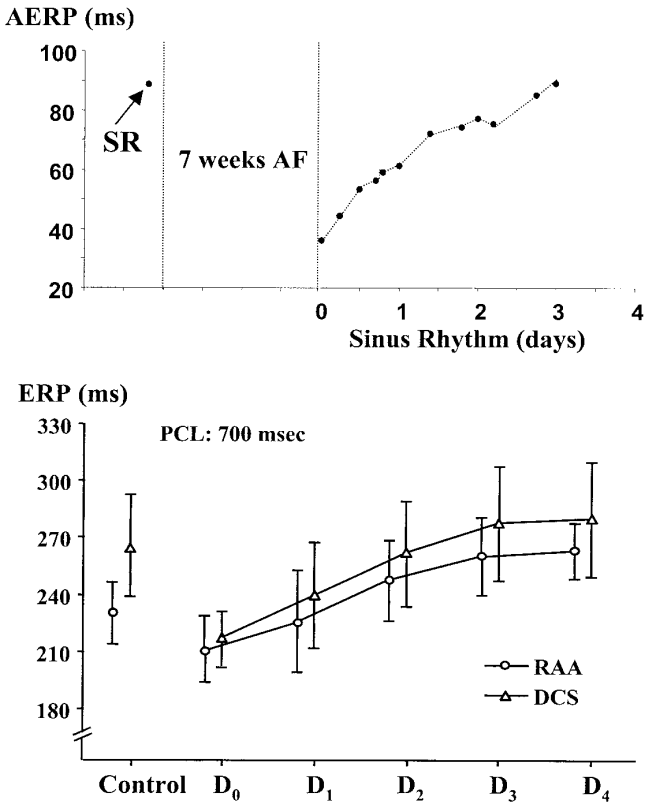


Fig. 4. Top: an example of reverse remodeling of the atrial effective refractory period (AERP) after conversion of 7 weeks of AF. Within 3 days of sinus rhythm the AERP returned to its control value (modified from Wijffels et al. [1]). Bottom: reversal of atrial electrical remodeling after cardioversion of long-term AF in man. Both in the right atrial appendage (RAA) and the distal coronary sinus (DCS) the refractory period gradually prolonged and reached control steady state values within 3 days of sinus rhythm. PCL, pacing cycle length; D, day (from Yue et al. [10]).

positive voltages, which increases rather than decreases the availability of these channels. It is equally unclear whether changes in atrial gap junctions may cause slowing of atrial conduction. First of all, the data on remodeling of the atrial connexins are not consistent. Elvan et al. [29] reported an increase in expression of connexin43 in dogs, whereas in humans a decrease in connexin43 was found [30]. In the goat model of AF Van der Velden et al. reported no change in connexin43 but instead a decrease and more heterogeneous distribution of connexin40 [31]. Second, although the gap junctions play a major role in conduction, the speed of propagation of the atrial impulse is only affected when the connexins are down-regulated by more than 40% [32]. Spatial heterogeneities in connexins might create microscopic obstacles for conduction which not necessarily disturb the conduction of a broad wavefront, but may serve as turning points or areas of zig-zag conduction when the wavefront becomes fragmented. It therefore remains a possibility that gap junctional remodeling is involved in

the creation of a substrate for persistent AF. Indeed, there are good reasons to believe that shortening of the atrial action potential is not the only factor involved in the development of permanent AF. The longer time course of the development of sustained AF and the cumulative effects of repetitive 1-month episodes of AF, strongly suggest that a much slower so-called 'second factor' is involved [1,33]. A good candidate for such a second factor is an increased tissue anisotropy due to changes in local expression of gap junctional proteins or tissue fibrosis as demonstrated in a canine model of heart failure [34]. In this model of heart failure induced by 5 weeks of rapid ventricular pacing, the atrial refractory period and spatial dispersion of refractoriness were not altered. Instead, discrete regions of slow conduction were the cause of the increased stability of AF. Such atrial remodeling of a 'different sort' could explain the development of a substrate for AF in old age, rheumatic valve disease and heart failure.

2. Contractile remodeling

Already more than 30 years ago Logan et al. documented that after cardioversion of AF the a-wave in the atrial pressure curve was lost (Fig. 5A) [35]. Using echocardiographic techniques, later studies revealed that this atrial contractile dysfunction correlated with the duration of AF and that it could take months before the atrial transport function was fully recovered [36,37].

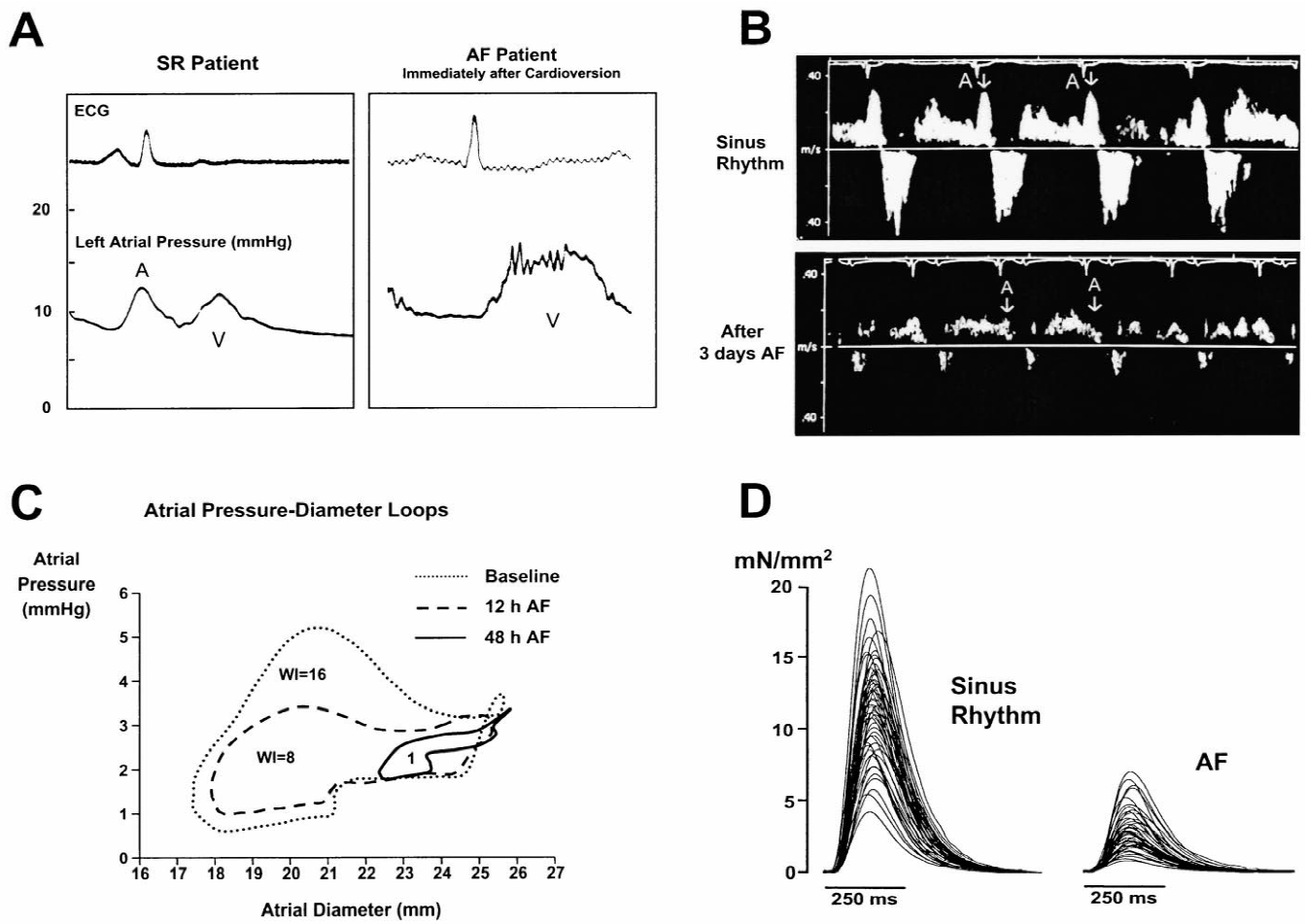


Fig. 5. (A) Left atrial pressure recordings of a control patient in SR and a patient immediately after cardioversion of chronic AF. The a-wave is completely abolished in the AF patient (modified from Logan et al. [35]). (B) Using a 7.5 MHz intravascular ultrasound probe (AcuNav®, Acuson Sequoia®) right atrial appendage Doppler flow velocities were measured before and after 3 days of lone AF in the goat. The white arrows point to the peak emptying flow during atrial systole (A). The peak emptying velocity of the right atrial appendage during atrial systole is clearly reduced after 3 days of AF. (C) Atrial pressure–diameter loops during atrial pacing at a cycle length of 400 ms. During the first 48 h of AF, the atrial work index (surface area of the pressure–diameter loop) diminished from 16 to 1 mmHg·mm. The almost completely closed loop after 2 days of AF indicates a virtually complete loss of atrial contractility. (D) Superimposed recordings of the force of contraction of small isolated right atrial trabeculae from 47 patients undergoing mitral valve surgery. In AF patients the average force of atrial contraction was reduced by about 75% (from Schotten et al. [48]).

Manning at al. showed that after 2 weeks of AF, recovery of atrial contractile function was complete within 24 h of sinus rhythm, whereas it took more than 1 month to recover from AF lasting more than 6 weeks [36]. Harjai et al. showed that patients undergoing electrical cardioversion displayed a greater degree of atrial dysfunction than those who were converted pharmacologically [38]. However, such a relationship between mode of cardioversion and atrial stunning was not confirmed by other studies. Even after spontaneous termination of AF a similar degree of atrial contractile dysfunction was demonstrated [39,40]. Although thromboembolic events often occur shortly after cardioversion they also may occur several days or weeks later [41]. Transesophageal echocardiography has shown that new atrial thrombi can be formed after cardioversion [42]. Thus, the depressed and slow recovery of atrial contraction after restoration of sinus rhythm may play a role in the occurrence of thromboembolic events, even when at the time of cardioversion atrial thrombi were not present [43].

The mechanisms responsible for the postfibrillatory contractile dysfunction are not completely understood. Originally it was thought that the electrical shock itself caused 'atrial stunning' [42], but soon it became clear that also after pharmacological and spontaneous cardioversion the contractile atrial function was depressed [39]. In experimental and clinical studies verapamil was able to largely prevent the atrial dysfunction after short periods of AF, indicating that atrial stunning is mediated by Ca^{2+}-overload [44,45]. While the altered atrial function after *short* paroxysms of AF is likely to be the result of changes in cellular metabolism, *long*-lasting atrial tachyarrhythmias may induce additional changes causing a more persistent atrial contractile dysfunction. In dogs with sustained atrial tachycardia (6 weeks) the degree of shortening of isolated atrial myocytes was shown to be reduced and associated with a pronounced reduction of the Ca^{2+}-transient [46]. In the same model the L-type Ca^{2+} current (I_{CaL}) was down regulated by 70% [10]. Since the I_{CaL} is a main factor in determining both the Ca^{2+} content and release from the sarcoplasmic reticulum, the down-regulation of I_{CaL} is expected to contribute to responsible for the AF-induced contractile dysfunction.

Presently, we are evaluating the development of atrial tachycardiomyopathy in the goat model of chronic AF [47]. Already after 3 days the atrial peak Doppler flow velocity was largely reduced during atrial systole, showing that atrial contractility was severely depressed (Fig. 5B). In Fig. 5C the changes in atrial pressure–diameter loops during the first 48 h of AF are shown. Already after 12 h the atrial work index was reduced by ~50%. After 2 days the atrial pressure–diameter loop became almost completely closed, indicating that during sinus rhythm or slow overdrive pacing the atrial contractions were nearly completely abolished. In two recent human studies we compared the force of contraction of small bundles of the right atrial appendage of patients undergoing mitral valve repair with and without long-standing AF [48,49]. In patients with chronic AF the contractile force was reduced by ~75% (Fig. 5D). Since the post-rest potentiation was fully maintained and also the relaxation velocity was still normal, a disturbance in Ca^{2+} reuptake by the sarcoplasmic reticulum could be excluded. In contrast, the positive inotropic effect of isoproterenol was markedly impaired although the density of the β-adrenoceptors and the expression of the inhibitory and stimulatory G proteins were unaltered. Also the catecholamine-stimulated adenylyl cyclase activity was not impaired showing that the β-adrenergic signal transduction was not desensitized [49]. Whereas in SR patients the L-type Ca^{2+} agonist Bay K8644 exerted a pronounced positive inotropic effect, in AF patients this stimulatory effect was only minor. Thus, in contrast to ventricular tachycardiomyopathy, which is due to a dysfunction of the sarcoplasmic reticulum and β-adrenergic desensitization, the atrial contractile dysfunction after prolonged fibrillation seems mainly to be due to a depressed L-type Ca^{2+} current.

3. Structural remodeling

The first study showing that AF causes alterations in the ultrastructure of atrial myocytes was that of Morillo et al. in 1995 [2]. In dogs subjected to prolonged periods of rapid atrial pacing (6 weeks), both light- and electronmicroscopic changes were found in the atria. Several later studies confirmed this important observation both in dogs and goats [29,50–54]. The alterations in atrial myocytes after sustained AF closely resemble the changes in ventricular myocytes due to chronic low flow ischemia (hibernation) [55]. Both in chronic hibernating ventricular myocardium and in fibrillating atria a phenotypic adaptation occurs towards a more fetal stage of development (dedifferentiation). The AF-induced structural changes in atrial myocytes include: (1) increase in cell size, (2) perinuclear accumulation of glycogen, (3) central loss of sarcomeres (myolysis), (4) alterations in connexin expression, (5) changes in mitochondrial shape, (6) fragmentation of sarcoplasmic reticulum, (7) homogeneous distribution of nuclear chromatin, and (8) changes in quantity and localization of structural cellular proteins (Fig. 6). Most prominent is an increase in atrial cell size associated with myolysis and perinuclear accumulation of glycogen. This hibernation of fibrillating atrial myocardium is heterogeneously distributed, with some cells strongly affected next to virtually normal cells. The dedifferentiation to a more fetal stage of development is evident from the re-expression of α-smooth muscle actin and the loss of desmin. In the goat, gap-junctional remodeling consists of a loss and heterogeneous distribution of connexin40. At an electron microscopic level changes in subcellular structures can be seen. In fibrillating myocardium nuclear chromatin is more

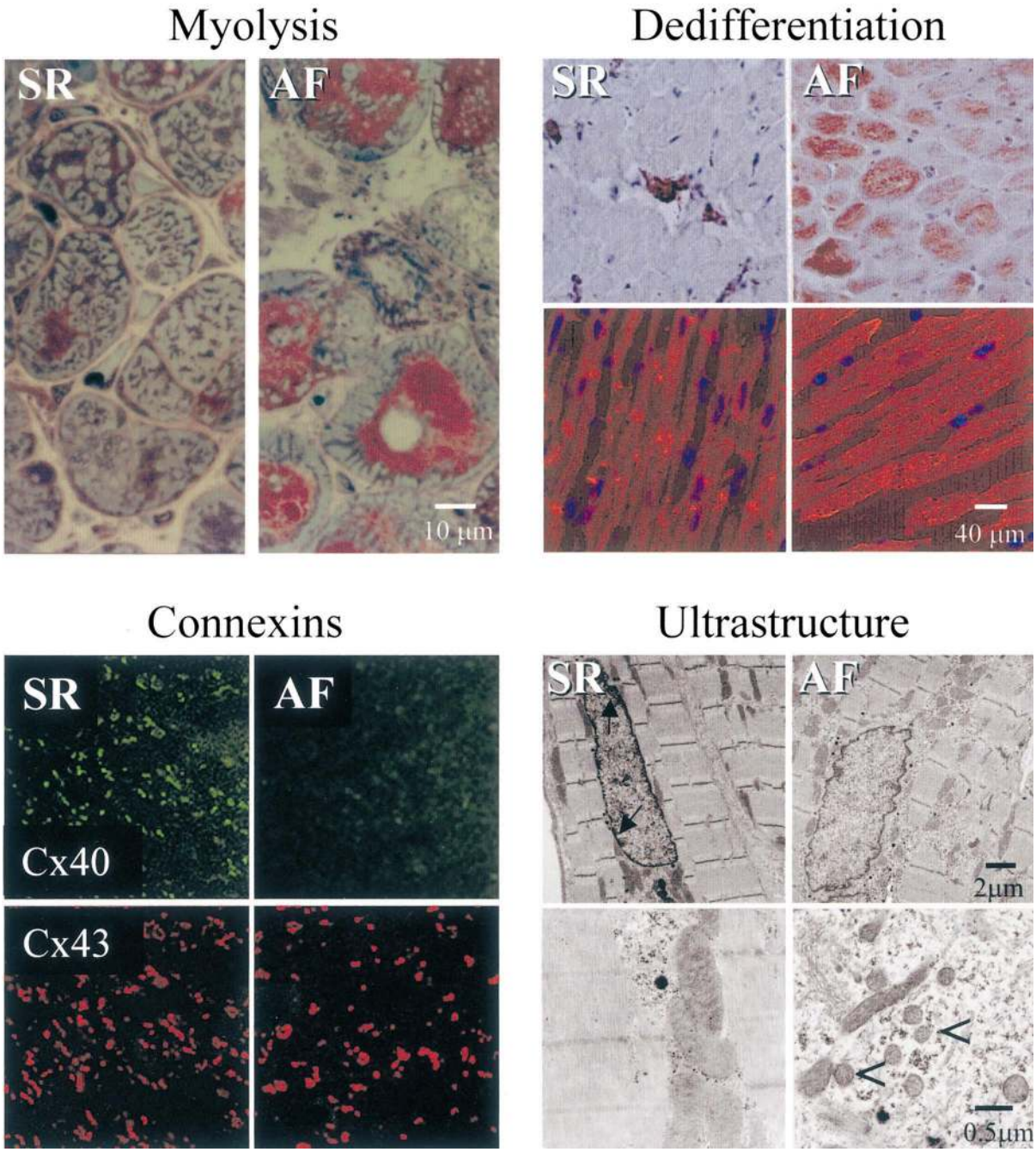


Fig. 6. Structural remodeling of atrial myocytes after 4 months of AF in the goat. The left pictures are taken from goats in sinus rhythm, the right photographs are from goats in chronic AF. Light microscopy (upper left panel) shows cells with severe myolysis (loss of sarcomeres: blue staining) and accumulation of glycogen (red). Immunostaining of structural proteins (right upper panel) demonstrates the dedifferentiation of the atrial myocardium by a clear increase in fetal α-smooth muscle actin (red staining in upper pictures). In the lower pictures of this panel the myocytes are stained for desmin (red). The nuclei are stained by blue DAPI. During AF desmin looses its cross-striated pattern in the cytoplasm and at the intercalated disks the intensified desmin staining is no longer present. In the lower left panel changes in gap-junctions are shown. Labeling of Cx40 (green) and Cx43 (red) revealed a clear reduction in Cx40 and no change in Cx43 expression. Electron microscopy (lower right) shows changes in the subcellular organization of the atrial myocytes. During AF the atrial nuclei get a more homogeneous distribution of chromatin For comparison the normal clustering of chromatin at the nuclear membrane is indicated by arrows in the upper left panel. During AF many small donut shaped mitochondria can be found (arrowheads right lower panel) (from Ausma et al. [50] and Van der Velden et al. [15]).

homogeneously distributed and the mitochondria are smaller with longitudinally oriented cristae.

Although in general the different animal models show similar structural changes, some differences exist between different species and different models of atrial tachyarrhythmias. In the dog, a high atrial rate is associated with

an increase in size of mitochondria [2], whereas in the goat model of AF numerous small mitochondria with longitudinally oriented cristae were found [50]. Whereas in models with pure atrial tachyarrhythmias the extracellular matrix was not changed [2,50], in canine atria subjected to a combination of rapid atrial pacing and mitral regurgitation, the volume of the intercellular space was increased [54]. The effects of structural remodeling on gap junctions also differ in different species [29,51].

These structural changes caused by AF should not be regarded as degenerative, since signs of irreversible changes leading to cell death (disruption of mitochondrial cristae, abnormal secondary lysosomes, cytosolic blebs, lipid droplets, discontinuities of the sarcolemma) and markers of apoptosis (bcl-2, P53, proliferating nuclear antigen, TUNEL reactivity) are all absent in chronic lone AF [52]. Instead, the structural changes in response to AF might be considered as the consequence of a physiological adaptation to chronic Ca^{2+} overload and metabolic stress. This is supported by the fact that after longterm AF the expression of heat-shock-proteins (HSP70, GRP94) is upregulated [56].

In patients, data about structural remodeling as a *consequence* of AF are still limited [48,57–59]. Only one study investigated the structural changes associated with lone AF [58]. Similar signs of dedifferentiation of human atrial myocardium were found as in various animal models. However, in patients with AF and atrial dilatation also degenerative changes were observed. Some nuclei of atrial myocytes showed a strong TUNEL reactivity indicative for DNA cleavage and programmed cell death [60]. Furthermore, the degree of interstitial fibrosis, both between individual myocytes (endomysial) and atrial bundles (perimysial) is increased in patients with chronic AF [57,59]. Compared to animal models, the more extensive structural changes found in patients might be related to the older age and/or associated heart diseases [48,61–66].

4. Relation between electrical, contractile, and structural remodeling

To study the relationship between electrical remodeling and loss of atrial contractility, goats were instrumented with epicardial electrodes and sonomicrometer crystals together with a right atrial pressure catheter [47]. During the first 5 days of AF, the atrial refractory period and work index were measured 30 min after spontaneous conversion of AF during regular atrial pacing. As expected, the refractory period shortened considerably from ~130 to ~80 ms (Fig. 7). Also the strength of the atrial contractions diminished and the atrial work index decreased from 16 to less than 2 mmHg·mm. After restoration of sinus rhythm this loss of atrial contractility completely recovered following the same time course as reverse electrical remodeling. After 2 days of SR both the atrial work index and the refractory period were back at control values. The fact that electrical and contractile remodeling go 'hand in hand', strongly suggests that they are the result of a common mechanism. Since electrical remodeling is known to be mainly due to a reduction of I_{CaL}, also atrial contractile remodeling is probably directly related to a reduction in Ca^{2+} inward current. However, so far the time course of AF-induced down-regulation of the I_{CaL} channels has not been directly compared with the time course of shortening of the atrial action potential and loss of contractility.

In humans, even after prolonged AF (months to years) electrical remodeling is completely reversible within a few

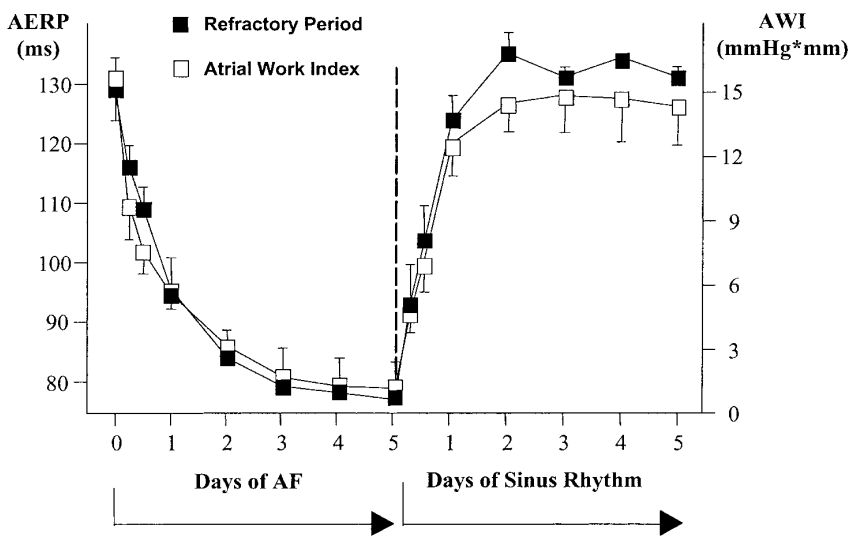


Fig. 7. Changes in atrial effective refractory period (AERP) and atrial work index (AWI) during 5 days of AF followed by 5 days of sinus rhythm in five chronically instrumented goats. During electrical remodeling and its reversal after cardioversion of AF, the changes in atrial work index followed the exact same time course as the changes in AERP (modified from Schotten et al. [47]).

days [28,67]. In contrast, depending on the duration of AF the recovery of the atrial transport function may take several months [36,37]. This delayed recovery of contractile remodeling suggests that, apart from the down-regulation of I_{CaL}, in *long-term* AF additional mechanisms are operative. One possibility is that the slow component of the recovery of atrial contractility reflects the slow re-synthesis of sarcomeres which have been lost during AF (myolysis) [48,50]. In a recent study we investigated the contribution of myolysis to the loss of atrial contraction in patients with and without chronic AF [48]. In patients with AF the contractile force of isolated right atrial trabeculae was reduced by 75% (Fig. 8). However, after increasing the Ca^{2+} concentration the maximal force of contraction was reduced by only 15%. Histological quantification of the degree of myolysis revealed a total reduction of sarcomeres of 14% (Fig. 8B). Thus, post-AF atrial stunning seems to be the result of two different mechanisms. The first and most important component is a functional loss of contraction due to decreased *activation* of the contractile apparatus due to the reduction of I_{CaL}. AF-induced atrial myolysis causes an additional 15% reduction in force of contraction. The functional part of atrial stunning recovers quickly (a matter of days) [47], whereas complete restoration of the atrial transport function in patients with chronic AF may take much longer (up to several months) [36]. Since the contribution of myolysis to the AF-induced atrial dysfunction is limited, most probably other, so far unidentified mechanisms are responsible for the delayed recovery of the atrial contractile function after cardioversion of prolonged AF.

In the 1980s Boyden and co-workers studied the relationship between atrial enlargement and electrophysiological properties in dogs and cats with mitral valve disease and ventricular cardiomyopathy [68–70]. In dilated atria increased amounts of connective tissue were found between enlarged myocytes. Also signs of degeneration and a loss of myofilaments were observed. These dilated atria had a high susceptibility for initiation and perpetuation of atrial arrhythmias. Transmembrane action potentials were not found to be significantly different from non-dilated atria. In a canine model of heart failure AF could be easily induced and was of long duration [34]. Also in these animals an increase in atrial size and extensive interstitial fibrosis was found. The main electrophysiological changes consisted of a marked increase in spatial heterogeneity in atrial conduction velocity. The susceptibility to AF in these models was explained by the increased interstitial fibrosis and a higher likelihood of local intra-atrial conduction block leading to smaller and more numerous reentrant circuits. Thus, both electrical and structural remodeling can either create a substrate for AF. The dimensions of intra-atrial circuits can become smaller either by shortening of the action potential (electrical remodeling) or by local conduction delay (enhanced nonuniform anisotropy). While electrical remodeling occurs in a couple of days, structural

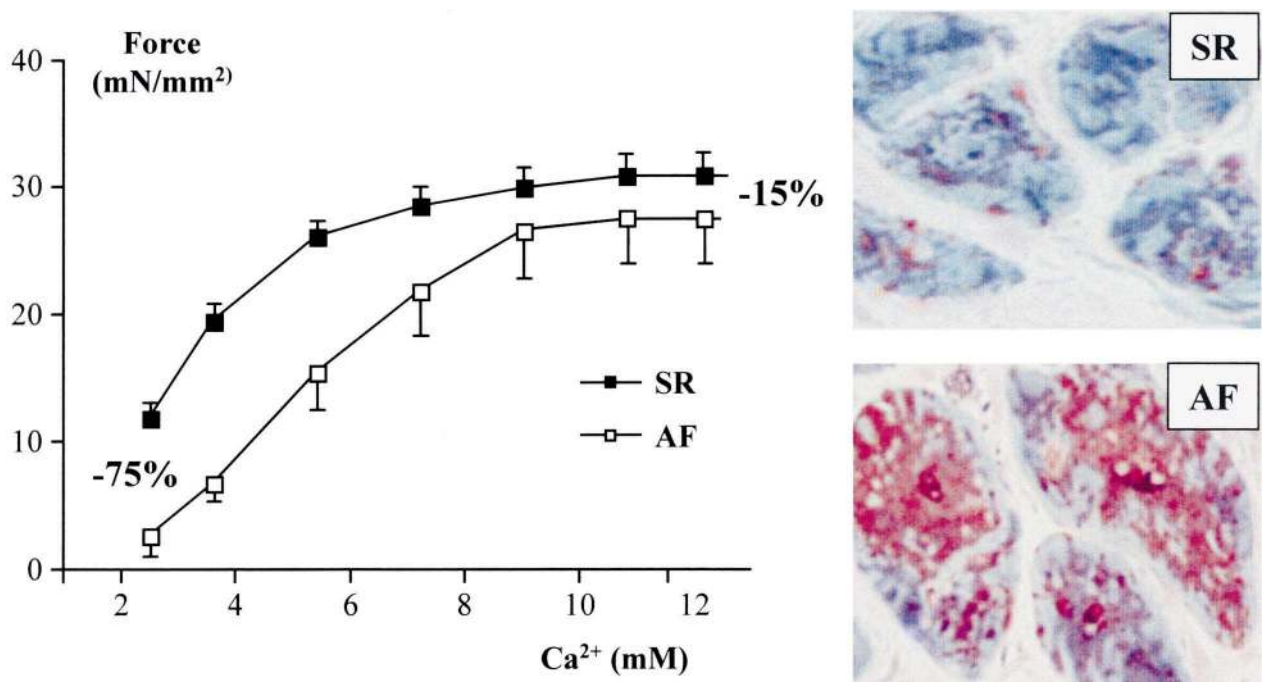


Fig. 8. The effects of extracellular Ca^{2+} concentration on force of contraction in isolated right atrial bundles from patients in sinus rhythm and chronic AF. At a physiological Ca^{2+} concentration of 2.5 mM, the force of contraction was 75% less in AF patients compared to SR patients. However, in both groups elevation of the extracellular Ca^{2+} concentration elicited a strong positive inotropic effect. This resulted in only 15% less contractile force at maximal activation by high Ca^{2+} in AF patients. The sarcomere content of the atrial myocytes (blue staining) was reduced to a similar extent (−14%). The red staining in the myolytic cells is due to glycogen accumulation (modified from Schotten et al. [48]).

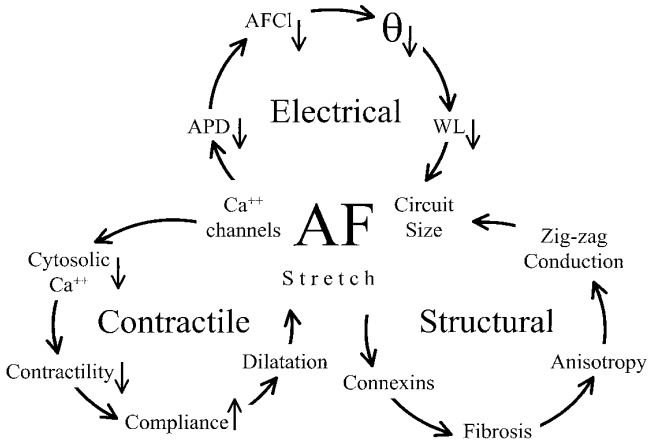


Fig. 9. Three proposed positive feedback-loops of atrial remodeling on AF. Down-regulation of the L-type Ca^{2+} channels is considered to be the primary cause for electrical and contractile remodeling. Stretch of the atrial myocardium, which is the result of loss of contractility and increase in compliance of the fibrillating atria, is hypothesized to act as a stimulus for structural remodeling of the atria. The resulting electro-anatomical substrate of AF consists of enlarged atria allowing intra-atrial circuits of small size, due to a reduction in wavelength (shortening of refractoriness and slowing of conduction) and increased non-uniform tissue anisotropy (zig-zag conduction).

remodeling is a much slower process which may continue for several months. In Fig. 9 the three cascades of electrical, contractile and structural remodeling are depicted. The positive feed back between electrical remodeling and AF is well established, whereas the proposed cascades of contractile and structural remodeling are still partly hypothetical. The electro-anatomical substrate of AF may consist of dilated atria with small local intra-atrial circuits, both due to shortening of refractoriness and increased non-uniform anisotropy. Increased non-uniform anisotropy may result from alterations in expression of connexins or atrial architecture (dissociation of atrial bundles, endo- and perimysial fibrosis).

5. Different time domains

5.1. The first minutes

Within the first minutes of AF, both the oxygen consumption and coronary flow of the atria increases nearly 3-fold [71]. Profound changes in atrial metabolism occur, which is expressed by a reduction in atrial creatine phosphate [45]. Due to the high rate, the cytosolic Na^+ and Ca^{2+} concentrations increase, the Ca^{2+} load of the sarcoplasmic reticulum rises [72] and moderate cellular acidosis develops. The increase in Ca^{2+} concentration contributes to the rate dependent shortening of the action potential by inactivation of the L-type Ca^{2+} channel. Also changes in the intracellular redox potential can inhibit the L-type Ca^{2+} channels [73]. After the onset of AF it takes several minutes before a new steady state in atrial refractory period, conduction velocity and ion concentrations is reached. Similarly, when AF terminates the action potential will only return gradually to its original shape, explaining why the refractory period is still short during the first minutes after conversion to sinus rhythm [74]. The changes in atrial contractility after termination of short-lasting AF are more complex. The first contractions are stronger than during steady state sinus rhythm due to the high intracellular Ca^{2+} concentration build up during the preceding AF episode [45]. However, already after a couple of seconds atrial contractility declines indicating that the Ca^{2+} overload disappears rapidly. Actually, the atrial contractions temporarily become 50% weaker than during steady state sinus rhythm (undershoot). Thereafter, the force of contraction gradually increases to its baseline value with a similar time course as the prolongation of the action potential [45,74]. Also in isolated atrial myocytes short-term rapid stimulation (3 min) results in a short period of hypercontractility, followed by a phase of hypocontractility before gradual recovery [72]. The major mechanism of the depressed cellular contractile function was a lowering of Ca^{2+} available for release from the sarcoplasmic reticulum.

Thus, after cardioversion of AF the early electrical and contractile changes of the atria have short on- and offset kinetics. As emphasized by Pandozi and Santini, these changes should be clearly distinguished from ‘true’ electrical and contractile remodeling which are based on alterations in gene expression with far slower kinetics. In this respect, the recently introduced terms ‘short-term remodeling’ [75] or ‘pseudo-remodeling’ [76] are somewhat confusing, since they actually have nothing to do with remodeling. The metabolic shortening of the atrial refractory period during AF may explain the higher vulnerability of the atria briefly after conversion to sinus rhythm [77]. In electrically remodeled atria, this transient metabolic shortening of the refractory period causes an additional shortening of the atrial action potential immediately after cardioversion of AF. The resulting temporary ultra-short refractory period provides a good explanation for immediate recurrences of AF (IRAF) frequently seen after electrical cardioversion [78,79].

5.2. The first days

During the first days of AF a progressive reduction in refractory period and atrial contractility occurs until after 3–5 days a new steady state is reached. Also reversal of this AF-induced electrical and contractile remodeling takes a couple of days [1,47]. This slower time course compared to the more rapid metabolically mediated changes, suggests that different mechanisms are involved. At present it is still uncertain whether the reduction in I_{CaL} is due to a decrease in the actual number of channels in the atrial cell membrane or to changes in channel properties. Also

insufficient knowledge exists about the exact time course in reduction of the I_{CaL} and the related AF-induced electrical and contractile remodeling. A direct correlation between the density of the L-type Ca^{2+} channels, the calcium inward current and atrial refractoriness was found by Gaspo et al. [80]. However, in this study it took several weeks of rapid atrial pacing for the atria to remodel, whereas in the goat model of AF electrical remodeling is complete within 3–5 days [1].

During the first days of AF the refractory period shortens considerably (20–40%), whereas after 6 weeks of rapid atrial pacing in the dog atrial conduction velocity was found to be moderately decreased [19]. Thus, as a result of electrical remodeling the wavelength of the atrial impulse shortens by a shortening in refractoriness and possibly also by slowing in atrial conduction. This shortening of the wavelength during AF allows more wavelets to coexist in the atria which can at least partly explain the increased stability of AF with time. Also, recurrences of AF are facilitated by electrical remodeling. In patients with chronic AF a positive correlation between the shortest coupling interval of premature atrial beats and early recurrence of the arrhythmia was found [81]. In humans with chronic AF it has been shown that the electrical remodeling of the atria (shortening of refractoriness) is completely reversible within 3 days of sinus rhythm [28]. This means that recurrences of AF occurring later than 3–5 days after cardioversion cannot be due to electrical remodeling. Recent experiments in goats have shown that also the contractility of the atria largely diminishes during the first days of AF. As a result, the compliance of the fibrillating atria will increase and the atria will dilate even when the mean atrial pressure does not increase [82].

5.3. The first months

There are reasons to believe that, besides the shortening of refractoriness also other factors play a role in the development of chronic AF. In the first study of Wijffels et al. in the goat in which 'AF begets AF' was demonstrated, it was already noted that the time course of the changes in atrial refractoriness did not run parallel with the increase in persistence of AF. Whereas the AF cycle length already reached a new steady state after 3–5 days, it took an additional 1–2 weeks before AF became persistent [1]. This led to the hypothesis that a so-called 'second factor' was involved in the development of persistent AF.

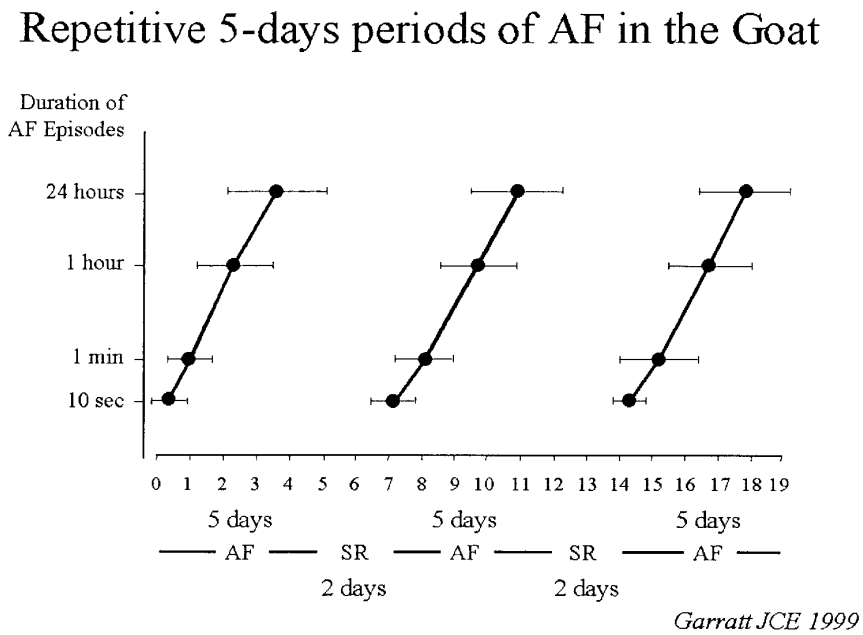
The time course of AF-induced structural changes in atrial myocytes has been extensively studied (Table 1) [83]. The first sign of structural remodeling is a more homogeneous distribution of nuclear chromatin resembling nuclei of embryonic myocytes and a decrease in the myocardial protein cardiotin. Both phenomena occurring after 1 week of AF are general signs of dedifferentiation and are not very likely to play a role in the stabilization of AF. In the time between 1 and 4 weeks of AF several additional changes occur such as a decrease and heterogeneous distribution of connexin40 (gap-junctional remodeling) [31], an increase in size of the atrial myocytes, loss of sarcomeres (myolysis) and perinuclear accumulation of glycogen. When AF continues for longer than 1 month a further increase in cell size, myolysis, glycogen accumulation and dedifferentiation occur. In addition, the sarcoplasmic reticulum became fragmented and the number of small mitochondria increase. After 4 months of AF the total amount of atrial connective tissue was not changed. However, because the atrial cells have become larger the amount of connective tissue per myocyte was increased.

The question whether the structural changes caused by prolonged AF are reversible or not, was addressed by two recent studies [54,84]. In the dog, 2 weeks after cardioversion of 8 weeks of AF combined with mitral regurgitation, no regression of the structural changes was yet observed. This was true despite the fact that by that time the AF-induced electrical remodeling was completely reversed [54]. From this study it is not clear whether absence of recovery of structural remodeling was due to the short time window studied or to the still existing mitral regurgitation, which in itself may cause tissue fibrosis. In the goat model of 16 weeks of lone AF, 8 or 16 weeks after cardioversion reversion of structural remodeling was still far from complete. Recovery of gap junctions occurred relatively rapid and the expression of connexin 40 was normalized within 8 weeks of sinus rhythm [84]. However, even after 16 weeks of sinus rhythm, many atrial myocytes were still myolytic and showed perinuclear glycogen accumulation.

Table 1
Time course of AF-induced structural remodeling

	1w AF	2w AF	4w AF	8 w AF	16 w AF
Nuclear chromatin	+	+	+	+	+
Downregulation of Cx40	+	++	++	++	++
Cell swelling/myolysis	+	+	++	+++	+++
α-Smooth muscle actin	+	+	++	+++	+++
Loss of cardiotin	+	+	++	+++	+++
Small mitochondriae			+	++	++
Remnants of SR			+	++	++
Loss of titin			+	++	+++
Loss of desmin				+	++

The hypothesis that a 'second factor' is involved in the development of persistent AF was recently tested by two studies (Fig. 10) [33,85]. In the first study, three successive 5-day periods of AF were maintained by burst pacing, each interrupted by 2 days of sinus rhythm. During these 2 days the electrical remodeling was completely reversed and the atrial refractory period returned to normal. It was hypothesized that, in case a 'second factor', repetitive AF episodes would exert a cumulative effect on the stability of AF. However, no significant differences were found in the time required for AF to become sustained during the second or third 5-day episode of AF. In a second study this protocol was repeated, but now the duration of the consecutive AF episodes was prolonged to 1 month. Following each month, AF was cardioverted electrically and the atrial refractory period was allowed to return to control before the next episode of AF. Although the time course of electrical remodeling was the same, the time required for development of persistent AF became shorter after each AF episode [33]. This evidence suggests that



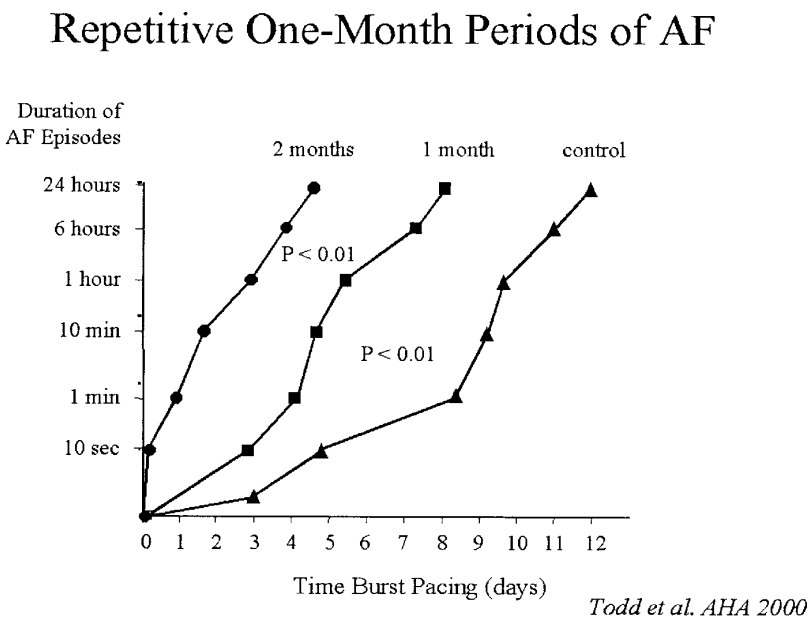


Fig. 10. Repetitive electrical remodeling by 5 days of AF interrupted by 2 days of sinus rhythm had no cumulative effect in the goat. In contrast, three consecutive 1-month episodes of AF resulted in a progressive shortening of the time required for the development of persistent atrial fibrillation. This strongly supports the hypothesis that a 'second factor' other than the atrial refractory period is involved in the remodeling process which creates a substrate for self-perpetuation of AF (from Garatt et al. [85] and Todd et al. [33]).

indeed a second factor is involved in the transition from paroxysmal to persistent AF. More evidence for the presence of a slow second factor was recently obtained by serial pharmacological cardioversion of lone AF. In goats without any underlying heart disease, the efficacy of cardioversion by class Ic drugs progressively reduced from 78% after 1 month to 30% after 4 months of AF [86]. Pharmacological cardioversion failed despite the fact that higher dosages of the drug were administered. Whereas a reduced efficacy of pharmacological cardioversion during the first days of AF is readily explained by electrical remodeling, failure in the course of several months of AF might be due to the much slower structural remodeling of the atria.

In patients AF has been related to the extent of structural changes [62] which were found to be a predictor for failure of cardioversion [61]. However, it is not easy to understand how certain changes in cellular structure like increased cell size, glycogen accumulation and different expression of structural proteins could play a role in perpetuation of AF. On the other hand structural changes in gap junctions and interstitial fibrosis might result in inhomogeneities in conduction. The enhanced nonuniform tissue anisotropy might be responsible for slow conduction and reentry which stabilize AF. The increase in atrial size due to loss of contractility will also increase the number of wavelets. Some studies showed that atrial enlargement was positively correlated to the recurrence of AF after conversion to sinus rhythm [87,88] and very recently, a significant correlation between atrial dimensions and the stability of AF was demonstrated in dogs with heart failure [89]. Regional differences in wall thickness resulting in inhomogeneous wall stress will further add to the increased heterogeneity in conduction. However, at the present time the exact nature of the 'second factor' involved in development of permanent AF is still unknown.

6. Future perspectives

New strategies for the management of AF, amongst other things, will depend on a better understanding of the mechanisms underlying atrial remodeling. In humans with chronic AF atrial electrical remodeling has been shown to be completely reversible within 3–4 days after cardioversion of AF [28]. Recurrences of AF are frequent during the first week after cardioversion and may be related to the process of reverse electrical remodeling [78,81]. Because of the short time course of AF-induced electrical remodeling and its complete and rapid reversibility, AF-recurrences occurring after 1 week cannot be explained on this basis. A persisting high susceptibility to AF might be due to structural remodeling of the atria as a result of prolonged AF. The reversibility of AF-induced structural changes has proven to be a very slow process which takes at least several months. Some structural changes may be even irreversible [84]. Thus the prevention of structural remodeling by AF might be an important new element in AF management. Recently, the ACE-inhibitor enalapril was shown to attenuate atrial fibrosis and conduction abnormalities in a canine model of heart failure [90]. Activation of the renin–angiotensin system causes atrial cell growth, proliferation of fibroblasts and atrial fibrosis. This might explain why ACE-inhibitors are effective to prevent AF in patients with heart failure [91] and left ventricular dysfunction after myocardial infarction [92]. Thus, whereas electrical remodeling is 'forgiving' and only plays a short-lasting role in the occurrence and perpetuation of AF, structural atrial remodeling may be less reversible. Thus, conservation of the normal atrial size and architecture by preventing structural atrial remodeling due to AF and ventricular dysfunction seems of prime importance for the future management of AF.

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