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Cardiovascular Research 54 (2002) 315–324

Cardiovascular Research

www.elsevier.com/locate/cardiores

Review

Molecular mechanisms of remodeling in human atrial fibrillation

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Received 10 September 2001; accepted 10 December 2001

Abstract

An important acknowledgement of the last several years is that atrial fibrillation (AF) modifies the electrical properties of the atrium in a way that promotes its occurrence and maintenance. This arrhythmogenic electrophysiological remodeling is well established, but can not explain by itself that 'AF begets AF'. This review describes molecular changes involving rapid functional alterations and slower changes in protein expression that cause electrical remodeling and contractile dysfunction in AF. An important molecular feature of AF is the reduction in L-type Ca^{2+} channel function and protein expression. This reduction may serve to protect the cell against a potentially lethal Ca^{2+} overload resulting from the increased activation rate in AF. Further, the review discusses the possible role of proteolytic systems, notably the calpains, as a mechanism linking Ca^{2+} overload to reduced protein expression. Thus, it appears that the elaborate molecular changes in AF are directed primarily at protecting the myocyte from cellular stress. However, such early protection occurs at the expense of electrophysiological changes that promote the long-term maintenance of AF.

Keywords: Ion channels; Contractile function; Arrhythmia (mechanisms)

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans. Most frequently, AF occurs in conjunction with other cardiovascular disease, such as hypertension, ischemic heart disease, valve disease or cardiac failure. However, in 20–50% of the patients AF is not associated with any underlying disease [1]. One of the most intriguing properties of AF is its tendency to become more persistent over time [2]. Consequently, a large percentage of patients with paroxysmal AF will develop persistent AF [2]. Also, conversion to and maintenance of sinus rhythm by pharmacological or electrical methods becomes increasingly difficult the longer the arrhythmia exists [3].

Experimental and clinical studies point at two major mechanisms involved in the intrinsically progressive nature of AF. The first consists of a change in the electrical properties of the atrium, notably a shortening of the AERP and a loss of rate adaptation [4,5], and hence was named *electrical remodeling*. Furthermore, based on data from experimental models, it has been considered that AF is also associated with elaborate adaptive and maladaptive changes in tissue and cellular architecture [6,7]. By parallel, this type of change was denominated *structural remodeling*. Together, these mechanisms will increase the probability of generating multiple atrial wavelets by enabling rapid atrial activation and dispersion of refractoriness [8].

Having identified electrical and structural remodeling as general pathophysiological mechanisms in the progressive nature of AF, recent studies have attempted to detect the

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Time for primary review 36 days.

0008-6363/02/$ – see front matter
PII: S0008-6363(02)00222-5

underlying molecular mechanisms. So far, the molecular research has been focussed mainly at various ion-channels and at proteins involved in calcium homeostasis. The purpose of this review is to discuss the observed molecular changes in relation with the pathophysiological adaptations in human AF and point out future directions of research.

2. Protein remodeling

2.1. Ion-channels

An abrupt increase in heart frequency, like in AF, causes an immediate (within one action potential) and then a gradual (reaching steady state over several minutes) decrease in action potential duration (APD) [9]. The decrease in APD reduces the atrial effective refractory period (AERP) and shortens the wavelength for re-entry, thus facilitating the occurrence and maintenance of reentrant arrhythmias like AF. This short-term adaptation coincidences with functional changes in the L-type Ca^{2+} channel following calcium overload [10–12] which (most likely) underlie the changes in ADP [13,14]. In addition, longer periods of sustained atrial tachycardia induce further changes in electrical properties over a course of hours to days [4,15–17]. As opposed to short-term adaptations, long-term changes appear to be caused by regulation of ion channel density, which are related to modified protein expression (Fig. 1A,B) [10,18,19].

In human AF, the relationship between changes in AERP and ion channel protein expression was investigated by studying the regulation of L-type Ca^{2+} channel and several K^+ channels. A study in patients with persistent and paroxysmal AF demonstrated a positive correlation between the ion-channel protein expression of L-type Ca^{2+} channel and the AERP, but also with the rate adaptation to AERP (Fig. 2A,B) [5]. Patients with paroxysmal and persistent AF showed marked reductions in L-type Ca^{2+} channel protein expression [20]. Furthermore the reduced L-type Ca^{2+} channel protein levels were associated with short AERP and poor rate adaptation. The findings suggest that downregulation of the L-type Ca^{2+} channel underlies the electrical remodeling in AF. L-type Ca^{2+} channel amounts and activity in persistent AF have also been investigated with experimental binding and electrophysiology studies. Fig. 3 shows an analysis of the amount of reduction in L-type Ca^{2+} channel mRNA, protein and current in clinical and animal experimental studies in time. From these data it appears that the reductions in L-type Ca^{2+} channel occur much faster in the animal model compared to human AF. This is reflected by a reduction of 70% after 6 weeks of experimental AF. These changes seem postponed in human AF, as a 70% reduction in current density was found only after at least 18 months of AF. The latter may indicate that other (protective) adaptation mechanisms play a role in human AF.

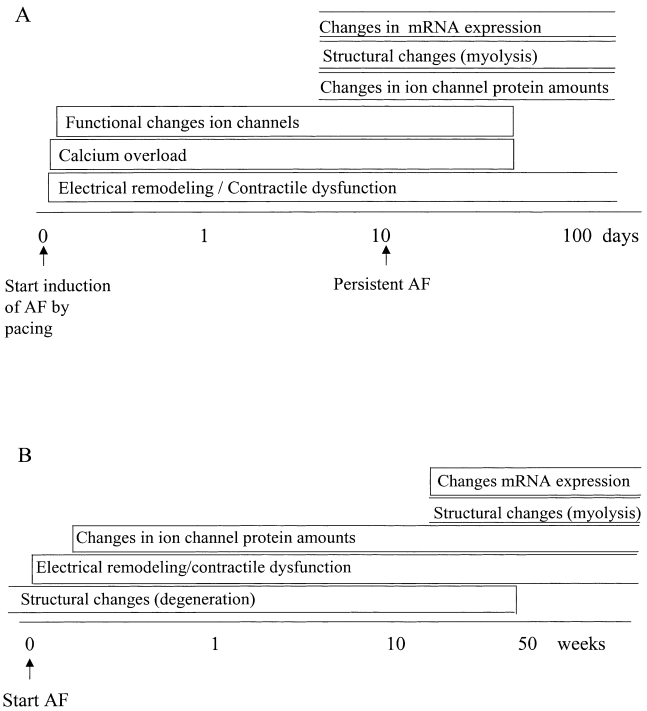

Fig. 1. (A) Conceptual overview of AF induced remodeling processes in experimental AF. (B) Conceptual overview of AF induced remodeling processes in human AF. Figures reproduced from thesis Brundel [50,96].

Since shortening of AERP can also be explained by increased K^+ conductance, a number of studies evaluated the expression levels of K^+ channels, notably Kv4.3, Kv1.5, HERG, minK/KvLQT1, Kir3.1/Kir3.4 and Kir6.2, in paroxysmal and persistent AF [5,21–24]. Remarkably, a reduction in mRNA and protein levels were found for several K^+ channels in patients with persistent AF, which is in plain contradiction with the shortening of AERP. The general interpretation of these results is that the electrophysiological changes in AF are primarily caused by the reduction in L-type Ca^{2+} channel [5,18]. Secondary to this process, the reduced expression of K^+ channels may serve to adapt the myocardial cell to the high rate and counteract the shortening of AERP [5].

Of note is the observation from one electrophysiological study, in which increased I_{KACh} and I_{K1} currents were found in isolated human atrial cells of patients with persistent AF due to different underlying heart diseases [23]. The apparent inconsistency between the reduction in K^+ channel protein levels and increased current densities can be explained by assuming changed single channel properties, such as an increase of mean open-time or channel conductance or a change in voltage dependency. Alternatively, this inconsistency may be attributed to variations in patient population and drug therapy. Changes in single-channel properties of K^+ channels await experimental confirmation.

While it is clear that protein expression of various ion-channels is modified during human AF, estimation of

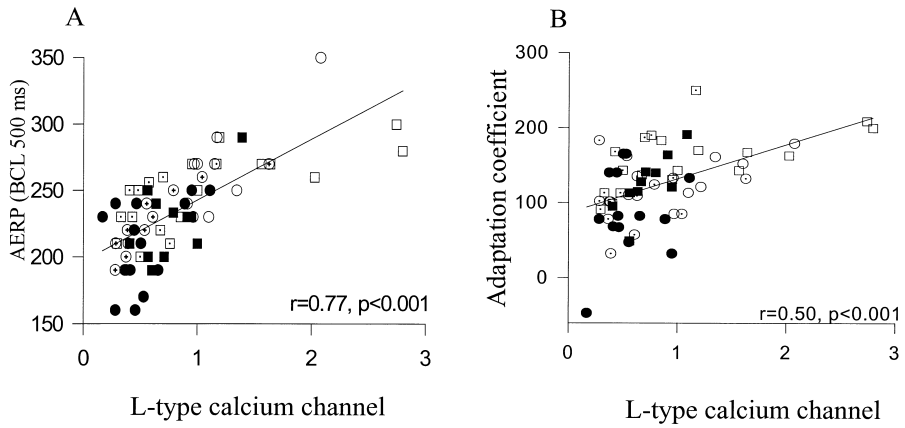

Fig. 2. (A) Correlation between the L-type Ca^{2+} channel protein expression and the AERP measured at basic cycle length of 500 ms in right and left atrial appendages. (B) Correlation between the L-type Ca^{2+} channel protein expression and the rate adaptation coefficient. (○) represents control patients in sinus rhythm undergoing CABG, (⊙) patients with lone paroxysmal AF, (●) patients with lone persistent AF, (□) patients in sinus rhythm with underlying mitral valve disease, (⊡) patients with paroxysmal AF and mitral valve disease, (■) patients with persistent AF and mitral valve disease (reproduced from Ref. [5]).

its time course depends largely on data from experimental studies. A study in dogs subjected to rapid atrial pacing for 7 and 42 days [10,18] demonstrated that high rate atrial stimulation does not change a variety of currents, including inward and delayed rectifier K^+ currents, T-type Ca^{2+} current, and Ca^{2+} dependent Cl^- current. Yet the about 70% reduction in L-type Ca^{2+} current (I_{CaL}) and transient outward K^+ current (I_{To}) observed after 6 weeks of rapid atrial pacing can be totally explained by reductions in channel protein levels [18,25]. In accord, channel properties of I_{CaL} and I_{To}, like voltage, time and frequency dependence are unchanged. Despite the quantitatively similar reduction in I_{CaL} and I_{To}, it has become clear that reduction in I_{CaL} plays the central role in the changes in APD caused by the atrial tachycardia [10].

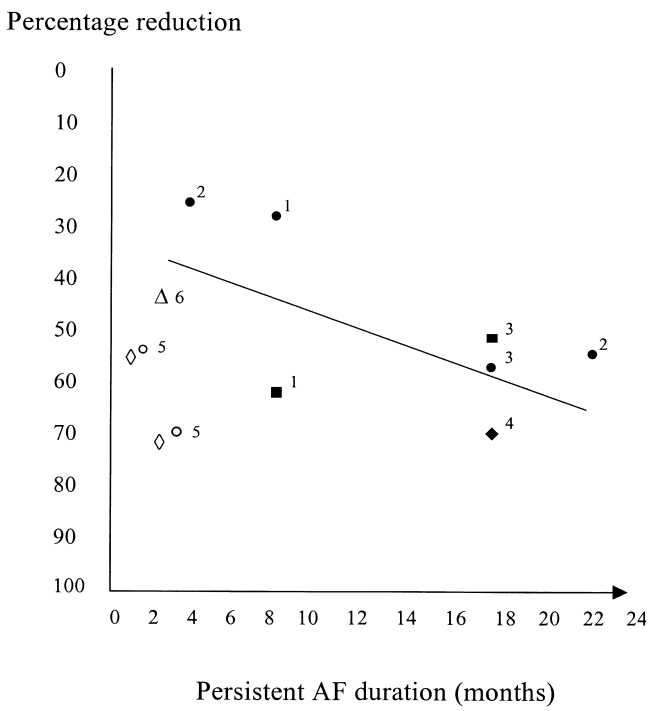

Fig. 3. Summary of changes in L-type Ca^{2+} channel gene expression and function. (●), mRNA amount human study (1 [5], 2 [29], 3 [19]) (○), mRNA amount experimental study (5 [10,18]; (■), protein amount human study (1 [5], 3 [29]); (♦), amount current human study (4 [20]); (◇), amount current experimental study (5 [10,18]); (△), experimental binding study (6 [25]). Figure reproduced from thesis Brundel [50,96].

Finally, studies on I_{Na} in atrial myocytes of dogs subjected to rapid atrial pacing indicate a gradual reduction in current density over time [26]. This reduction parallels those in conduction velocity, suggesting that alterations in I_{Na} contribute to the conduction changes associated with sustained atrial tachycardia. Changes in the expression of the Na^+-channel in human AF have only been documented on the mRNA level so far. The mRNA level was found unaffected in persistent AF and 35% upregulated in paroxysmal lone AF [5]. Clearly, the determination of the role of the Na^+-channel in human AF awaits determination of changes on the protein level.

In recent years, it has become clear that electrical remodeling is paralleled by a more or less general reduction in ion-channel protein levels as part of the adaptation mechanisms during AF. Since the reduction in ion-channel protein expression was supposed to occur due to the AF, this phenomenon was called ion-channel remodeling. It seems likely that ion-channel remodeling plays an important role in the susceptibility to AF after restoration of sinus rhythm, especially the occurrence of IRAF (immediate reinitiation of AF) and subacute relapses. It may be hypothesized that reduced ion-channel protein expression persist for some time after restoration of sinus rhythm, thereby creating a highly arrhythmogenic substrate due to changes in cellular electrophysiological and possibly also mechanical function. In the presence of such a substrate

only a single atrial premature beat may induce a relapse of AF.

2.2. Proteins influencing calcium homeostasis

Animal experimental studies show that electrical remodeling of the atrium occur within several days after the onset of AF (Fig. 1A) and the cessation of contractile properties of the atrium within several hours [4,27,28]. Both are largely attenuated by blocking the L-type Ca^{2+} channel, indicating that changes in the calcium homeostasis play a pivotal role in the induction of atrial electrical remodeling and contractile dysfunction. This observation has prompted research on the molecular remodeling of proteins which influence calcium homeostasis [19,29–31]. One of the main findings of these human studies was the reduction in mRNA and protein expression of the L-type calcium channel (see above). Examination of additional gene products only revealed a decrease in sarcoplasmatic reticulum Ca^{2+} ATPase (SR Ca^{2+} ATPase) mRNA and protein levels, predominantly in patients with persistent AF. However, no changes in mRNA expression were found for phospholamban, sodium–calcium exchanger, ryanodine receptor 2, and calsequestrin [19,29–31]. Taken together, these studies show that changes occur in the protein expression of proteins influencing the calcium homeostasis in persistent human AF, although they are so far limited to the L-type Ca^{2+} channel and SR Ca^{2+} ATPase. However, given their importance in contractile function, such changes probably represent a contributory factor for the atrial contractile dysfunction in AF.

2.3. Connexins

Since AF is promoted by slow conduction [15,16,32,33] a number of studies have focussed on gap-junction proteins, which play an important role in rapid and homogenous propagation of the wavefront in the heart [15,34–36]. Gap-junctions are clusters of connexin-channels, which span the closely opposed plasma membranes forming cell-to-cell pathways. Connexins are permeable to ions and small molecules up to 1 kDa in molecular mass, including second messengers such as inositol triphosphate, cyclic AMP and calcium. The initial data presented on changes in intercellular connexins seemed contradictory. One study in the dog showed that AF increases connexin43 expression, the most abundant connexin [15], while another study in goat suggested that connexin43 is unaltered, but that the distribution of its atrial isoform, connexin40, was altered [35]. In a recent goat study, the gap junctional changes in relation to stabilization of AF were studied [34]. While in sinus rhythm a homogeneous distribution of connexin40 was found, a marked heterogeneity was observed after 2 weeks of AF, by the time intracellular Ca^{2+} is deposited [37] and just before AF became sustained. Moreover, the connexin40 distribution pattern correlated with the occurrence of structural changes (myolysis) in atrial myocytes and might be involved in the pathogenesis of sustained AF [34]. Thus, these animal experimental results suggest that heterogeneity of connexin distribution, rather than simple up- or down-regulation, may play an important role in the susceptibility to AF.

3. Electrophysiological remodeling

Over the past several years, AF-induced electrical remodeling have been studied in substantial detail (for review see [17,38]). In brief, experimental studies have identified part of the underlying electrophysiological changes explaining the progressive nature of AF [4,32]. The increased tendency of the atria to fibrillate is paralleled by a shortening of the atrial effective refractory period (AERP) and loss of the physiological rate adaptation of the refractory period which was termed atrial electrical remodeling [4]. The reduction in rate adaptation of the AERP is also observed in patients with AF [39]. All studies have shown that sustained atrial tachycardia decreases AERP and changes occur over a period of days to weeks [4,15,16,32], however, AF can decrease AERP over a time interval as short as several minutes (Fig. 1A,B) [12]. Although the AERP reduction caused by AF favors arrhythmia maintenance, it seems not the only factor involved because AF-induced AERP alterations become maximal well before AF-promoting effects stabilize [4,16]. One of the AF-promoting effects is tachycardia induced atrial conduction slowing [15,16,32], which has a slower time course than AERP changes. This might be due to a delayed onset of changes in Na^{+} channel expression [18] or gap junction remodeling [34,35], which could account at least for a part of the continued development of susceptibility to AF once AERP changes have stabilized.

In addition to changes in the absolute value of AERP, atrial tachycardia also affects the spatial distribution of AERP. The spatial heterogeneity of AERP appears to be an important determinant in the maintenance of AF [40–43] possibly due to changed atrial autonomic innervation [44].

The combination of electrophysiological changes caused by sustained atrial tachycardia i.e. reduced AERP, diminished or reversed adaptation to rate, slowed conduction and increased spatial AERP heterogeneity, and the underlying ion-channel protein remodeling changes would be expected to promote AF maintenance by enhancing the number of functional re-entry circuits during AF.

4. Structural remodeling

In addition to electrophysiological, functional ion-current and ion-channel gene expression changes, AF is associated with adaptive and maladaptive alterations in

morphology [6,7,45–47]. In patients with atrial arrhythmias, myolysis and glycogen storage (adaptive features) are only observed in a small number of cells and frequently accompanied by lysosomal degeneration (maladaptive features) [7]. In experimental models, these structural abnormalities appeared to be more pronounced when the underlying pathology was aggravated by sustained AF [48,49]. The occurrence of degenerative myocardium could lead to increased dispersion of refractoriness and conduction, which was found to enhance the inducibility and spontaneous occurrence of idiopathic human AF [43] (Fig. 1B). Taken together, the observed structural changes are indicative of a substantial deterioration of normal tissue architecture, likely to promote AF through heterogeneity of atrial refractoriness [42,43] and slowed atrial conduction [15,16,32].

In their goat model, Ausma et al. noted mitochondrial enlargement, glycogen accumulation, loss of sarcoplasmic reticulum and contractile elements in the atria of goats subjected to chronic AF for up to 23 weeks [6]. These changes resemble those observed in the hibernating myocardium of patients [50,51]. Recently, the time course of structural changes during AF in goats after 1–16 weeks of AF was studied [52]. Here, the structural changes appeared to develop progressively, the earliest changes found after 1 week of AF represented by nuclear redistribution of heterochromatin (Fig. 1A). By then, the nuclei show a homogeneous distribution of chromatin, resembling a pattern found in embryonic/neonatal cardiomyocytes [6,46]. From 4 weeks onwards, AF affects structural features of sarcomeres, glycogen, mitochondria and sarcoplasmatic reticulum simultaneously. The loss of sarcoplasmatic reticulum and contractile proteins may negatively influence contractile force and lead to atrial stunning [52].

5. Underlying molecular mechanisms

As described in the previous sections, AF induced changes in the expression of multiple proteins are the likely mechanisms which promotes the susceptibility of the human atrium to the arrhythmia. Often, the level of protein expression is controlled by the rate of transcription of its mRNA from the genetic material. Consequently, changes in protein levels will be accompanied by similar changes in mRNA. However, this appears not to be always the case in AF. A marked discrepancy between changes in mRNA and protein levels were found in various studies in experimental and human AF [5,21,34,53,54]. Whereas ion-channel protein levels were substantially decreased, the mRNA levels were essentially unaffected. A number of mechanisms may be implicated, such as activation of mRNA silencers, a general reduction in translation efficiency or activation of protein degradation (proteolysis). The latter seems the most likely mechanism, as very recently increased proteolytic activity due to activation of calpains was found in atrial tissue of patients with paroxysmal and persistent lone AF (Fig. 4A) [50]. The increased proteolytic activity was predominantly due to increased calpain I expression (Fig. 4B). Furthermore, the increased calpain I protein was localized at the nucleus and intercalated discs of atrial myocytes. Finally, a correlation between calpain activity and protein levels of L-type Ca^{2+} channel was found. In addition, calpains have been reported to mediate cell death in metabolically inhibited cultured rat cardiomyocytes and are involved in troponin proteolysis and cross-linking following cardiac stunning and calcium overload [55–57].

Although a causal relationship between calpain activation and regulation of protein expression controlling the remodeling in AF has not been proven yet, it seems an attractive hypothesis. Since calpains are activated by an increase in cytosolic calcium, this hypothesis would link calcium overload, which is perceived as one of the most important features of AF [37,58], to the molecular changes observed in AF. Calpains are calcium-activated neutral proteases [59], which cleave mainly cytoskeletal and membrane-associated proteins into ‘limited fragments’ without further degradation [60]. Calpains have been implicated in the degradation of the L-type Ca^{2+} channel [61–63], cytoskeletal proteins [64] but also proteins directly involved in excitation-contraction coupling [65]. At the nucleus [66] calpain can induce degenerative features leading to cell death, which is also observed in human AF [7,67]. Since extreme cellular stress, in combination with sustained elevated cytosolic calcium levels, as in experimental AF [37] often results in necrosis, calpain may play an important role in this condition [68]. Whether gap junctional remodeling may be caused by calpain induction is unknown, but it is known that at least proteasome activity underlies a connexin43 degradation [69].

On the other hand, the crucial role of cytosolic calcium increase, in particular calcium overload, in the changes induced by AF has been recognized widely. Atrial contractile dysfunction occurs both after short-term and after chronic AF [70–72] (Fig. 1A,B). The explanation for the atrial dysfunction after short-term AF might be an increase in cytosolic Ca^{2+} due to the high rate of atrial activation [12,17,27,28,73–75]. Fast successive action potentials inhibit a proper sarcoplasmic reticulum Ca^{2+} re-uptake, resulting in elevated cytosolic Ca^{2+}, impairing the excitation-contraction coupling and contractile function [37,51,58,76]. Contractile dysfunction after chronic AF is most likely related to the cellular alterations in atrial myocytes [19,29] reflected by structural alterations, probably induced by proteolysis. In experimental AF, Ausma et al. showed sarcolemma-bound Ca^{2+} and Ca^{2+} deposits in mitochondria to increase markedly up to 2 weeks and tends to regress towards normal levels at 4 and 8 weeks of AF (Fig. 1A) [37]. Unfortunately, their methods used limit the visualization of Ca^{2+} load at subcellular sites like the sarcoplasmic reticulum. Additional data, however, show

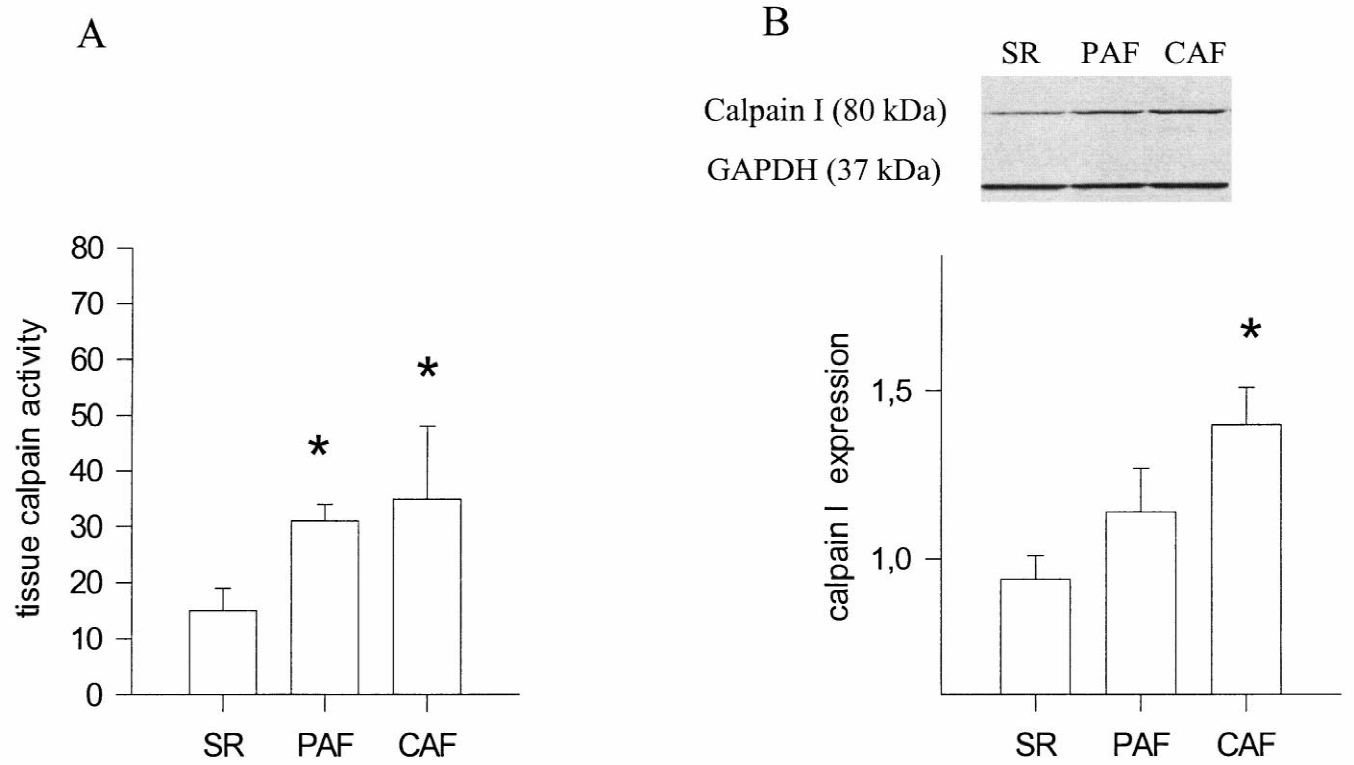

Fig. 4. Significant increase of tissue calpain activity (A) in right atrial appendages of patients with sinus rhythm (SR), paroxysmal AF (PAF) and persistent AF (CAF). (B) Western-blot of calpain I expressed as ratio to GAPDH and group protein ratios for calpain I. *$P<0.01$ compared to SR. Calpain activity was expressed as nM AMC/mg protein/30 min.

that atrial tachycardia causes an immediate increase in cytoplasmic Ca^{2+} concentration, which results in impaired Ca^{2+} release and cellular contractile dysfunction after the cessation of tachycardia [58]. In addition to the L-type Ca^{2+} channel, T-type Ca^{2+} channels may be implicated in atrial tachycardia-induced electrical remodeling, because the T-type Ca^{2+} channel blocker mibefradil limits both the ERP changes and AF promotion caused by 1 week of rapid atrial pacing. Also in this case calcium overload would be prevented by blocking a calcium channel [77].

Apart from calcium overload, atrial ischemia has been put forward as an underlying mechanism explaining the cellular ultrastructural changes caused by sustained human AF because of its resemblance with the hibernating myocardium [6]. Whether ischemia occurs in AF is still debatable, but a reduced atrial blood flow in dogs with rapid pacing induced AF was found and may result in atrial ischemia [78]. A potential role for atrial ischemia is consistent with the protective effect by blockade of the Na^+/H^+ exchanger in short term tachycardia-induced atrial electrophysiological remodeling [79] and contractile dysfunction [80]. In this model, ischemia would give rise to a decrease in intracellular pH, which leads to an exchange of intracellular hydrogen ions for extracellular Na^+ ions. Such an increase in intracellular Na^+ results in 'reverse-mode' functioning of the Na^+/Ca^{2+} exchanger and therefore an influx of Ca^{2+} ions [81]. Alternatively, inhibition of the Na^+/H^+ exchanger may alter cellular ionic homeostasis and combat calcium overload induced by ischemia.

Thus, several lines of evidence point to a central role for intracellular calcium overload in AF induced remodeling. Recent results reveal the potential role of calcium sensitive processes that lead to changes in protein expression and structural changes [50]. Because elevated levels of intracellular Ca^{2+} are known to activate proteolysis, this could result in increased breakdown of myofilaments [57,82] and ion-channel proteins [5]. In turn this might be responsible for decreased contractility as well as for the remodeling processes that convey the vulnerability to AF.

6. Substrate for AF

The purpose of this review is primarily to describe the molecular mechanisms related to the progressive nature of AF. However, a recent approach in molecular AF research is to target the underlying substrate for the arrhythmia [75]. These substrates have been studied in patients and experimental models with underlying cardiac disease promoting AF. For instance, atrial fibrosis in the failing heart provides a pathophysiologic substrate for AF [83,84]. Furthermore, recent studies provide evidence for the promoting action of atrial fibrosis by enhanced extracellu-

lar signal-regulated protein kinase (ERK) activation [85] and angiotensin receptor changes [53] in human AF. An experimental study demonstrated angiotensin-converting enzyme inhibition to counteract development of the AF substrate in dogs with congestive heart failure [86]. These results suggest that changes in the atrial angiotensin and ERK systems may be mechanistically related to AF-promoting electrical [83] or structural remodeling.

7. Possible clinical relevance

The probability of successful chemical or electric cardioversion is dependent on the duration of AF. The clinically observed diminished efficacy of cardioversion after long term AF cannot only by explained by the occurrence of electrical remodeling. The ion-channel protein remodeling and structural remodeling probably also affect the electrophysiological function of the atrial myocardium. In patients with persistent AF, there is a correlation between the duration of AF and the time needed to recover atrial contractile function after cardioversion [71,84]. The increase in calpain activity which could lead to structural remodeling of the atrial myocytes might offer an explanation for the delay in recovery of contractile function in the atria after conversion to sinus rhythm as seen in patients with persistent AF. Interference with the calpain pathway by pharmacological means may represent a novel therapeutic strategy to decrease protein degradation and thereby reduce the vulnerability to AF. Calpain inhibitors are as therapeutic agents already used in nerve and muscle degeneration [85], but their potential benefit in heart diseases is not studied yet. After restoration of normal sinus rhythm it may require the cardiomyocytes a certain period to rebuild a normal amount of sarcomeres, if that is still possible at all [45]. Unfortunately, data on the recovery of ion-channel protein expression after cessation of AF are still lacking. However, a few reports describe reversal of electrical remodeling in human AF after cardioversion, such in contrast to the absence of reversal of structural changes [86–89]. Since AF induces remodeling in the atria it is essential to restore sinus rhythm as soon as possible, thereby preventing the continuation of the atrial structural, ion-channel protein and electrical remodeling. On the other hand, identification of the mechanisms underlying protein remodeling in AF may enable successful ‘priming’ of a patient prior to cardioversion.

8. Future research

Research on AF focussed mainly on describing electrical remodeling, contractile dysfunction and structural changes. Functional experiments were designed to block electrical remodeling and contractile dysfunction. Possibly studying the intracellular pathways which are activated by electrical stress lead to the adaptive and maladaptive, degenerative structural changes [90,91]. One of the possible important roles might be for the calcium overload induced proteolytic activity. This postulation is supported by recent views on the dominant role of calpain in forms of apoptosis and necrosis through the degradation of cytoskeletal and contractile proteins, and activation of caspases [92–95]. These pathways may open new avenues for understanding the pathophysiology of AF and perhaps additional pharmacological interventions.

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