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Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure

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Abstract

Objective: Atrial remodeling contributes to the maintenance of atrial fibrillation (AF) in several cardiac disorders. There is evidence that angiotensin-converting enzyme (ACE) inhibitors reduce the prevalence of AF in patients with congestive heart failure (CHF). There have been no studies performed to assess the effects of ACE inhibitors on atrial dimensions and emptying function in relationship to vulnerability to AF in the setting of experimental CHF. **Methods:** CHF was produced in 20 dogs by rapid right ventricular pacing during 5 weeks. The dogs were randomized to enalapril (EN) therapy (2 mg/kg/day, $n=10$) or to a control group ($n=10$). Echocardiography was performed at baseline and weekly thereafter. At the 5-week electrophysiological study, AF was induced by burst pacing and AF duration was measured. **Results:** Atrial areas increased significantly with CHF. Left atrial (LA) fractional area shortening (FAS) decreased by 42% ($P=0.0001$) in controls but by 9% ($P=$NS) in the EN group ($P=0.01$, EN vs. controls). Similar findings were observed for right atrial (RA) changes ($P=0.02$). Atrial fibrosis was highly correlated with the decrease in LA FAS ($r=0.85$, $P<0.01$) and was reduced by EN (from 11.2 ± 1.6 to $8.3\pm0.7\%$, $P=0.008$). AF duration was 720 ± 461 s for controls and 138 ± 83 s for EN ($P=0.001$). LA and RA areas and FAS at 5 weeks correlated with AF duration ($P\leq0.001$ for all). FAS decrease in both atria also correlated with AF duration at follow-up ($r=0.78$ and 0.77 for LA and RA, $P\leq0.001$ for both). **Conclusions:** Experimental CHF causes structural and functional abnormalities in both atria, which are correlated with AF duration. ACE inhibition attenuates CHF-induced atrial fibrosis and remodeling and reduces associated AF promotion. These results indicate a role for the renin–angiotensin system in arrhythmogenic atrial structural remodeling in CHF. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: ACE inhibitors; Arrhythmia (mechanisms); Atrial function; Fibrosis; Heart failure; Remodeling; Supraventr. arrhythmia

1. Introduction

Congestive heart failure (CHF) is a particularly common cause of sustained atrial fibrillation (AF) encountered in clinical practice [1–6]. In patients with symptomatic heart failure, the prevalence of AF ranges from 10 to 30%, with the highest incidence among those with the most severe heart failure [4,5]. On the other hand, AF promotes heart failure: in patients with CHF, cardiac index and peak exercise oxygen consumption decline and functional class worsens when AF occurs [7]. Experimental CHF induced by rapid ventricular pacing produces abnormal local atrial conduction properties associated with atrial structural changes, including extensive interstitial fibrosis, enlargement and hypertrophy [6,8]. This atrial structural remodeling increases the ability of atria to sustain AF [6].

The importance of the renin–angiotensin system in the pathophysiology of ventricular remodeling and heart failure has been extensively described [9]. Angiotensin-converting enzyme (ACE) inhibitors attenuate left ventricular remodeling after myocardial infarction, and improve ventricular performance, symptoms, and prognosis in patients with left ventricular dysfunction. More recently, one study showed that the ACE inhibitor trandolapril reduced the incidence of AF in patients with systolic dysfunction after myocardial infarction [10]. We have recently shown that ACE inhibition reduces extracellular signal-related kinase (ERK) activation and atrial remodeling in experimental

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CHF [11]. However, the effects of ACE inhibition on CHF-induced changes in atrial functional remodeling in relationship to AF promotion have not been evaluated. Thus, the purpose of this study was to determine: (1) the relationship between CHF-induced structural and functional abnormalities of the atria as assessed by echocardiography and histology; (2) whether these abnormalities correlate with AF inducibility; and (3) whether the ACE inhibitor enalapril prevents atrial structural and functional abnormalities and attenuates atrial vulnerability to AF in CHF.

2. Methods

2.1. Animal preparation

The investigation conformed with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). We used a dog CHF model produced by rapid right ventricular pacing as previously described [12]. A ventricular pacemaker (model 8084, Medtronic) was implanted in a subcutaneous pocket in the neck under pentobarbital anesthesia (30 mg/kg, i.v.) and attached to a pacing lead in the right ventricular (RV) apex. The pacemaker was programmed to capture the RV at 240 beats/min (bpm) for 3 weeks, followed by 2 weeks at 220 bpm, to diminish early death from severe heart failure. CHF was established by clinical signs (lethargy, dyspnea and edema) and confirmed by hemodynamic measurements and echocardiographic studies. Twenty mongrel dogs were randomized to the enalapril ($n=10$) or to the control group ($n=10$). The dosage of enalapril was 2 mg/kg/day, p.o., started on the day of pacing and given for 5 weeks.

2.2. Transthoracic echocardiography

Serial transthoracic echocardiographic studies were performed at baseline ($n=10$ for each group) and after 1 week ($n=10$ for each group), 2 weeks ($n=9$ in controls; $n=8$ in enalapril group) and 5 weeks ($n=8$ in controls; $n=9$ in enalapril group) of pacing. Dogs were placed in left lateral decubitus position, and sedated with Atravet (0.07 mg/kg) and buprenorphine (0.009 mg/kg) i.m. for serial echocardiographic examinations. Each examination was performed with the pacemaker off and with the dog in sinus rhythm. We used a 2.5-MHz phased-array transducer and a standard echocardiographic system (Hewlett-Packard, Andover, MA, USA). The apical 4- and 2-chamber views were obtained and recorded on videotape for off-line measurements. Special care was taken to obtain similar imaging planes on serial examinations. The operator and investigator were blinded to treatment assignment during the whole study course.

For both the left atrium (LA) and right atrium (RA),

areas in both cardiac systole (defined as the largest) and cardiac diastole (defined as the smallest) were measured in the apical 4-chamber view. The average of three consecutive cardiac cycles were used for each measurement. Atrial fractional area shortening (FAS) was calculated as (systolic area−diastolic area)/systolic area×100.

In order to validate our measurements, we subjected ten echocardiograms to three repeated readings in a blinded fashion, with three consecutive cardiac cycles analyzed during every reading of each recording. The intercycle coefficient of variation [(S.D./mean)×100%] between three consecutive cardiac cycles of the ten echocardiograms averaged 3.2±1.5 and 5.4±2.1% for LA and RA areas in cardiac systole, and 3.6±2.5 and 6.0±4.2% for LA and RA areas in cardiac diastole, respectively. The coefficient of variation among the three separate blinded readings, each based on the average of three cycles, averaged 1.6±0.6 and 3.3±2.3% for LA and RA areas in cardiac systole, and 2.3±1.2 and 4.3±2.7% for LA and RA areas in cardiac diastole, respectively. Good correlations have been previously described between measurements of LA areas and LV end-diastolic pressure [13].

Left ventricular (LV) end-diastolic and end-systolic volumes were measured using the biplane Simpson's method of discs. The LV ejection fraction was calculated as the difference between both volumes divided by the LV end-diastolic volume times 100.

2.3. AF inducibility and AF duration assessment

After 5 weeks of RV pacing, the dogs were anesthetized with morphine (2 mg/kg, s.c.) and α-chloralose (120 mg/kg, i.v., followed by 29.25 mg/kg/h) and ventilated to maintain physiological arterial blood gases. A median sternotomy was performed. The implanted pacemaker was deactivated, and five silicon sheets containing 240 bipolar electrodes were attached. Stimulation and recording were performed as previously described [6,14]. The effective refractory period (ERP) was measured at left atrial and right atrial appendages, with 15 basic (S1) stimuli followed by a premature (S2) stimulus, with S1S2 decreasing by 5-ms decrements. The ERP was defined as the longest S1S2 interval that failed to produce a propagated response. Conduction velocity was measured in the right and left atrial free wall after 2 min at each basic cycle length as previously described [6]. AF was induced by premature stimuli and burst pacing, with up to three consecutive extrastimuli at a basic cycle length of 360 ms and then atrial burst pacing of 10 Hz for 1–10 s. AF was considered sustained if it required electrical cardioversion for termination (cardioversion was never performed until ≥30 min had passed since AF onset). To estimate the mean duration of AF, AF was induced ten times if AF duration was <20 min, and five times if AF lasted between 20 and 30 min. When electrical cardioversion was applied, a 30-min rest period was allowed before the experiment was continued.

2.4. Microscopic examination

In a total of eight dogs (four in each group), atria were immersed in 10% neutral-buffered formalin for 24 h. Samples were obtained from Bachmann's bundle, the appendages, the LA posterior and inferior wall, the crista terminalis and the RA free wall. From each zone, tissue blocks were collected following longitudinal and transverse planes. Sections (5-μm thickness) were cut at room temperature and stained with Masson trichrome, and fibrous tissue content measured by quantitative image analysis as previously described [6,15]. Briefly, microscopic images were scanned into a personal computer with Scion IMAGE software. IMAGE files were analyzed with SIGMASCAN 4.0 (Jandel Scientific). Connective tissue was quantified on the basis of its color with a color discrimination algorithm subjected to manual verification, and was expressed as a percentage of the reference tissue area. Blood vessels and perivascular interstitial cells were excluded from the connective tissue quantification.

2.5. Statistical analysis

All data are expressed as mean±S.D., except in figures (for which 95% confidence intervals are shown). To analyze evolution over time of variables studied, mixed-model repeated-measures analysis of covariance controlling for the baseline value [16] were used to extract the group×time interaction and the time and group main effects. When the group×time interaction was significant, which means that groups showed a significant difference in evolution, slice effect (also known as simple effect) [17] analyses were performed to evaluate differences among groups at each time level and to test the evolution of each group. These analyses were performed with the MIXED procedure of SAS 6.12 to handle missing data. Pearson's correlation coefficient was used to evaluate the relation between atrial variables and AF duration. A P value <0.05 was considered statistically significant.

3. Results

There was one death (at 2 weeks) in the enalapril group and two deaths (one at 2 weeks and one at 5 weeks) in the controls due to severe heart failure. There was one pacemaker failure at 2 weeks in the enalapril group, which was corrected and the dog paced up to 5-week follow-up. Mean AF duration was not recorded in two dogs in the enalapril group and one dog in the control group.

3.1. Echocardiographic results

LA and RA systolic and diastolic areas increased from baseline to 5-week restudy in both groups, with all P values ≤ 0.0001. The increase in LA systolic area was

similar in both groups, as was the case for RA systolic area. In contrast, LA diastolic area increased by 68% in enalapril-treated dogs (from 7.8 ± 1.5 to 13.2 ± 5.1 cm^2) and by 80% in control dogs (from 7.7 ± 2.3 to 14.9 ± 4.0 cm^2), and RA diastolic area increased by 36% (from 4.9 ± 1.4 to 6.7 ± 2.3 cm^2) and 61% (from 4.3 ± 1.6 to 7.5 ± 2.2 cm^2) in the enalapril and control groups, respectively.

The evolution of both LA and RA FAS over time was significantly different between both groups (Fig. 1). LA FAS decreased significantly over the study course by 42% in the control dogs (from 35.3 ± 2.5 to $20.2\pm4.5\%$, $P=0.0001$), but nonsignificantly by 9% in enalapril dogs (from 32.8 ± 3.1 to $29.8\pm8.9\%$, $P=0.169$). This difference in LA FAS decrease was highly statistically significant between treatment groups, with a P value of 0.01. Similar findings were obtained for the decrease in RA FAS. RA FAS decreased by 34% (from 37.9 ± 5.3 at baseline to $24.3\pm6.2\%$ at 5 weeks) in the control group ($P=0.0001$),
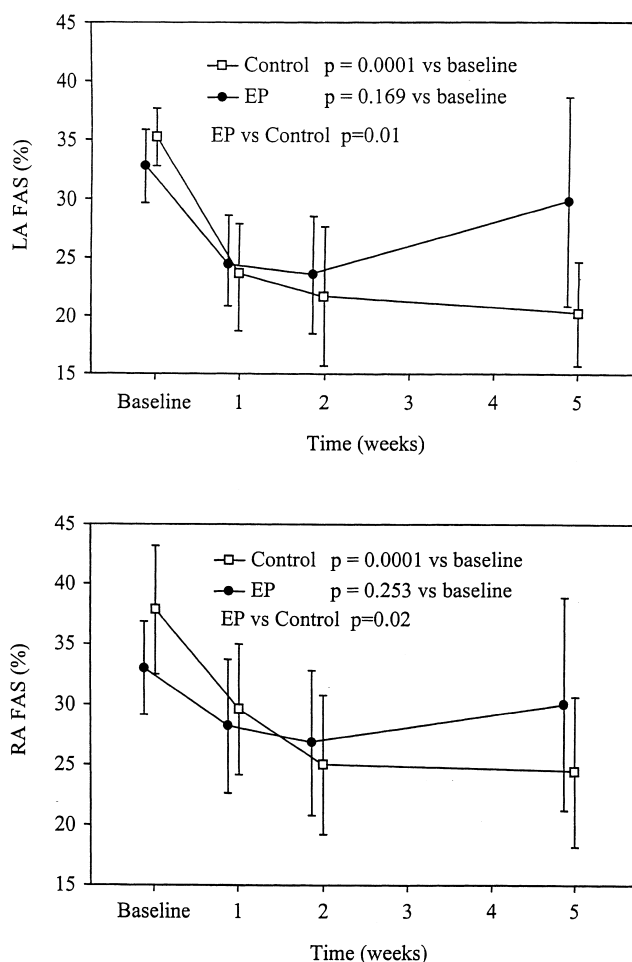

Fig. 1. Evolution of left atrial (LA, above) and right atrial (RA, below) fractional area shortening (FAS) in enalapril (EP) dogs vs. controls. LA and RA FAS decreased significantly over the study course in controls, but not in EN dogs (P values vs. baseline). This difference in evolution between treatment groups was statistically significant (EN vs. control).

but only by 7% (from 33.0±3.9 to 30.0±7.6%, *P*=0.253) in the enalapril group (*P*=0.02 for EN versus controls).

LV end-diastolic volume at baseline was 73.9±18.8 ml in enalapril-treated dogs and 78.5±27.1 ml in the control dogs (*P*=NS) and increased to 117.8±38.8 and 134.7±34.4 ml at 5 weeks (*P*=0.18 for enalapril versus controls). In contrast, LV end-systolic volume was 30.2±6.9 and 32.2±11.7 ml in the enalapril and control groups at baseline (*P*=NS) but increased respectively to 69.1±32.1 and 92.1±25.3 ml at 5-week restudy (*P*=0.06, enalapril versus controls). As a result, LV ejection fraction decreased by 25% (from 58.7±3.7 to 43.0±8.6%) in enalapril dogs and by 47% (from 59.3±3.9 to 31.8±7.8%) in controls (*P*=0.005, enalapril vs. controls).

3.2. Hemodynamic and histologic measurements

LV end-diastolic pressure at 5 weeks was 21±1 mmHg in control dogs and 16±1 mmHg in enalapril-treated dogs (*P*=0.001). Similarly, mean LA pressure was 19±1 and 14±1 mmHg in the control and enalapril groups, respectively (*P*=0.001). Enalapril was also associated with an increase in systolic blood pressure (104±4 vs. 117±3 mmHg, *P*=0.05). The percentage of atrial fibrosis was

Fig. 3. Correlation between AF duration and atrial fractional area shortening (FAS) at 5-week restudy. LA, left atrium; RA, right atrium.

significantly reduced by therapy, from 11.2±1.6% in the control group to 8.3±0.7% in the enalapril group (*P*=0.008). Atrial fibrosis was highly correlated with LA FAS at 5 weeks (*r*=−0.77, *P*<0.01) and with the decrease in LA FAS (*r*=0.85, *P*<0.01) from baseline to restudy.

3.3. Electrophysiological assessment

AF duration at the end of the study was significantly different between treatment groups. Mean AF duration was 138±83 s in the enalapril group and 720±461 s in the control group at 5-week follow-up (*P*=0.001). AF duration correlated with atrial systolic and diastolic areas at 5-week restudy, with *r* values of 0.64 and 0.78 for LA and 0.66 and 0.77 for RA (*P*≤0.01 for all correlations, Fig. 2). Negative correlations were observed between AF duration and atrial FAS at 5 weeks for both the LA (*r*=−0.79) and RA (*r*=−0.71) (*P*<0.01 for both, Fig. 3). AF duration was also correlated with the decrease over the study course of both LA and RA FAS (*r*=0.78 and 0.77, respectively, *P*≤0.001 for each, Fig. 4).

In contrast, enalapril did not have an effect, when compared to placebo, on effective refractory period
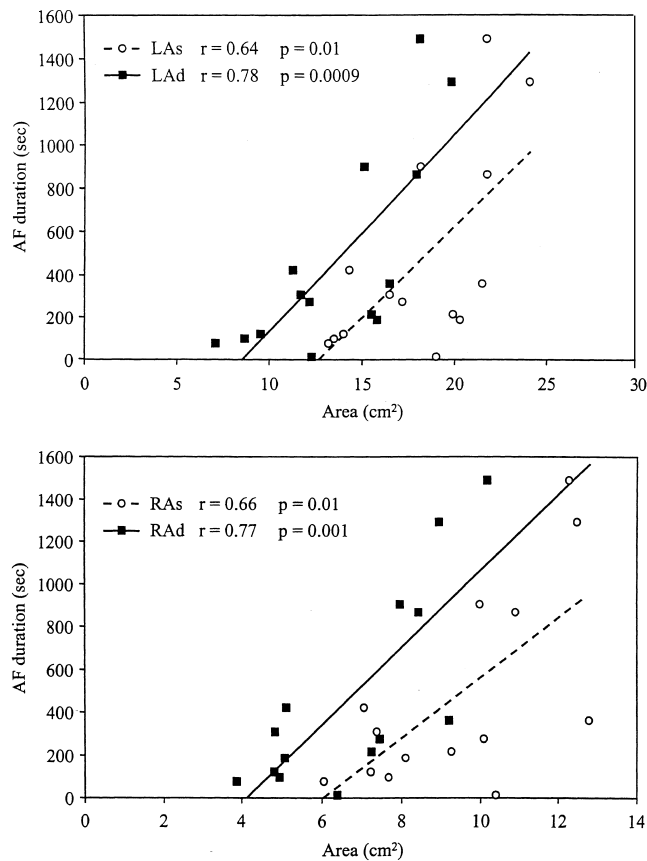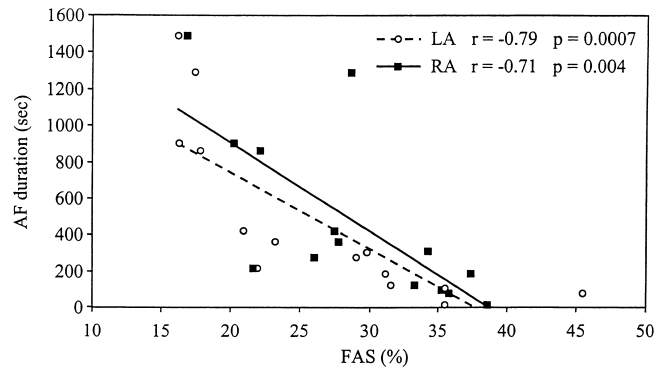

Fig. 2. Correlation between atrial fibrillation (AF) duration and both left atrial (LA, above) and right atrial (RA, below) areas at 5-week restudy. s, cardiac systole; d, cardiac diastole.
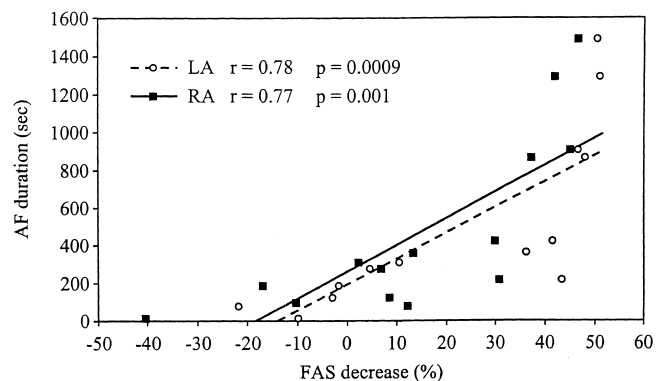

Fig. 4. Correlation between AF duration and the decrease of atrial fractional area shortening (FAS) between baseline and final examination. LA, left atrium; RA, right atrium.

(147±23 vs. 140±22 ms, $P=0.52$), conduction velocity (105±11 vs. 106±7 cm/s, $P=0.85$) or wavelength (15.5±3.0 vs. 15.1±2.5 cm, $P=0.79$) at a BCL of 350 ms.

4. Discussion

The results of this study show that experimental CHF creates substantial atrial structural and functional remodeling as assessed by echocardiography, with increased atrial dimensions and decreased fractional area shortening. Both atrial structural and functional remodeling correlated with vulnerability to AF in the setting of CHF. We also found that enalapril significantly attenuated both atrial functional remodeling, with much less LA and RA FAS decrease over the study course in dogs treated with the ACE inhibitor than in controls, and atrial fibrosis.

4.1. Atrial remodeling and fibrosis in experimental CHF and AF

Power et al. [18] reported an approximately 100% increase in LA cross-sectional area obtained from a long-axis view in diastole, in a 6-week right ventricular pacing ovine CHF model. The increase in LA area obtained in the apical 4-chamber view in cardiac diastole in our 5-week ventricular pacing CHF dog model was of a similar order (80% in the control group). Our study differed from that of Power et al. in that we also analyzed atrial systolic area, introduced FAS to this model, related atrial structural and functional changes to AF duration, and evaluated the effects of enalapril. Echocardiographic characteristics of the RA had also not been described in Power's and other previous studies [6,12,18]. In addition, we have shown the relation between echocardiographic and histologic changes. Indeed, the decrease in atrial FAS was highly correlated with the extent of atrial fibrosis in our study.

Marked atrial interstitial fibrosis is an important feature of AF associated with CHF [6,19,20]. In contrast to chronic atrial tachycardia, which promotes AF maintenance by reducing the wavelength for reentry and increasing the regional disparity of refractoriness, CHF does not alter these variables in a fashion that would be expected to favor AF [6]. Rather, the key changes in atrial electrophysiology caused by heart failure appear to involve alterations in local atrial conduction properties caused by atrial structural remodeling and interstitial fibrosis [6]. These abnormalities represent the substrate that increases the atrial ability to sustain fibrillation in the failing heart. Our observation in the present study of a good correlation between atrial structural and functional remodeling on echocardiography and AF duration in CHF dogs is consistent with this notion and supports the rationale for intervening at the level of the structural substrate in order to prevent AF.

4.2. Renin–angiotensin system and atrial remodeling and fibrosis

It has been well established that the renin–angiotensin (AT) system is important in the process of ventricular remodeling associated with CHF [9]. Furthermore, ACE inhibition and AT-1 receptor blockade prevent collagen accumulation in the non-infarcted myocardium after myocardial infarction in rats [21,22]. The fibrotic abnormalities associated with isoproterenol-induced CHF are also limited by AT-1 receptor inhibition [23]. Finally, AT-II has been shown to promote collagen synthesis by cultured fibroblasts and to reduce collagenase activity [24].

The signal transduction systems responsible for the atrial remodeling and fibrosis associated with AF are not well known. AT-1 receptors have been shown to be downregulated and AT-2 receptors upregulated in patients with AF, and the expression of ACE was found to be increased [25,26]. We have shown atrial MAP kinase activation in CHF-related AF remodeling, with ERK appearing particularly important as a target of the renin-AT system [11]. In addition to attenuating FAS decrease in both atria and reducing atrial fibrosis, enalapril reduced AF duration in experimental CHF in the present study. Our results support those obtained with another ACE inhibitor, trandolapril, which was shown to decrease the incidence of AF in patients with LV dysfunction [10].

4.3. Potential clinical relevance

Currently used antiarrhythmic agents to prevent AF alter atrial electrophysiological properties but are associated with the risk of potentially lethal proarrhythmia. ACE inhibition is a potentially appealing approach to treating AF associated with CHF, because of the lack of potential proarrhythmic effects. Although most CHF patients who can tolerate it are treated with an ACE inhibitor, dosages used are frequently small [27]. Our study may provide the impetus for studying the clinical value of ACE inhibitors used at high dosages or in combination with an AT-1 receptor blocker to prevent CHF-induced AF. ACE inhibitors may also be effective at preventing AF in other settings, such as hypertension, rheumatic valve disease and the aging process, if they can be shown to be associated with a similar substrate. Whether interfering with the renin–angiotensin system can reverse arrhythmogenic atrial remodeling and fibrosis once established is not known. Brilla et al. recently demonstrated that lisinopril could induce regression of ventricular fibrosis in patients with hypertensive heart disease [28]. In contrast, captopril did not reduce myocardial fibrosis when therapy was begun after CHF had developed in spontaneously hypertensive rats [29]. Serial echocardiographic examinations in the same animals over time could uniquely demonstrate whether ACE inhibition can induce reverse remodeling of the atria. In conclusion, our results indicate a role for the

renin–angiotensin system in arrhythmogenic atrial re-modeling in CHF, and a possible new approach to preventing the development of the substrate for AF.

Acknowledgements

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