Angiotensin-(1–7) prevents atrial fibrosis and atrial fibrillation in long-term atrial tachycardia dogs

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**A B S T R A C T**

Renin–angiotensin system (RAS) is activated in the fibrillating atria. Angiotensin-(1–7) [Ang-(1–7)] counter-balances the actions of angiotensin II (Ang II). To investigate the effects of Ang-(1–7) on the long-term atrial tachycardia-induced atrial fibrosis and atrial fibrillation (AF) vulnerability, eighteen dogs were assigned to sham group, paced group, or paced + Ang-(1–7) group, 6 dogs in each group. Rapid atrial pacing at 500 bpm was maintained for 14 days, but dogs in the sham group were instrumented without pacing. During the pacing, Ang-(1–7) (6 μg·kg⁻¹·h⁻¹) was given intravenously. After pacing, atrial mRNA expression of ERK1/ERK2 and atrial fibrosis were assessed, the inducibility and duration of AF were measured. Compared with sham, ERK1/ERK2 mRNA expression was increased in the paced group (P<0.05). Atrial tissue from the paced dogs showed a large amount of interstitial fibrosis, and the inductive rate of AF was increased at various BCLs in paced dogs (P<0.01). Compared with the paced group, Ang-(1–7) prevented the increase of ERK1/ERK2 mRNA expression (P<0.01 and P<0.05, respectively), and attenuated the interstitial fibrosis (P<0.01). Inducibility and duration of AF were reduced by Ang-(1–7) at various BCLs. In conclusion, Ang-(1–7) reduced AF vulnerability in chronic paced atria, and antifibrotic actions contributed to its preventive effects on AF.

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**1. Introduction**

The renin–angiotensin system (RAS) has been shown to be involved in many cardiovascular diseases. Atrial fibrillation (AF) is associated with activation of the RAS in the atria in humans and in a dog model of AF [1]. In patients undergoing cardiac surgery, patients with a history of paroxysmal or persistent AF had tissue levels of angiotensin-converting enzyme (ACE) that were three-fold higher compared with those in sinus rhythm [2]. In ventricular tachypacing-induced congestive heart failure animal model of AF, atrial angiotensin II (Ang II) concentration was increased [3]. Willems et al. [4] established that the development of AF by atrial tachypacing was associated with an increase in plasma level of Ang II in a sheep model. AF is known to produce structural remodeling of the atria (i.e., fibrosis) [5]. Atrial fibrosis, a frequent finding in patients with AF, may lead to persistent susceptibility to AF [6]. Ang II is a potent promoter of fibrosis, it triggers the mitogen activated protein kinase (MAPK) pathway [2,3], which is responsible for the proliferation of fibroblasts and hypertrophy of cardiomyocytes [7]. Increased amounts of collagen and cellular hyperplasia of fibroblasts cause separation of atrial myocytes—which slows intra-atrial conduction—and induce regional conduction block, which is the ideal condition for the onset and perpetuation of AF [8–10].

The RAS is classically described as a circulating enzymatic pathway of which the sole product of importance is the vasoactive peptide Ang II. Although Ang II plays a key role in the biology of the RAS, it is certainly not the only biologically active peptide produced by this system, particularly within tissues. In addition to being a substrate for Ang II production, angiotensin I (Ang I) can also be converted by neutral endopeptidase to angiotensin-(1–7) [Ang-(1–7)] [11]. Alternatively, Ang-(1–7) can be produced directly from Ang II by the carboxypeptidase ACE2, a homolog of ACE [12]. The recently discovered heptapeptide Ang-(1–7) appears to counterbalance most of the Ang II effects, such as vasoconstriction and hypertensive actions [11]. Santos et al. [13] made transgenic rats to suggest that Ang-(1–7) can be cardioprotective. Correlative studies have shown that Ang-(1–7) reversed cardiac hypertrophy and fibrosis [14–17]. Therefore, the purpose of the present study was to evaluate the effects of Ang-(1–7) on atrial fibrosis and AF vulnerability in the long-term atrial tachycardia dogs.

**2. Materials and methods**

**2.1. Preparation of the canine model**

We obtained experimental animal use approval by the Experimental Animal Administration Committee of Tianjin Medical University and Tianjin Municipal Commission for Experimental Animal Control. A previously described approach was used to produce dogs with the ability to maintain sustained AF [18]. For this study, eighteen mongrel
dogs of either sex, weighing between 12 and 17 kg, were randomly assigned to sham group, paced group, or paced + Ang-(1–7) group, 6 dogs in each group. The dogs were anesthetized with intravenous pentobarbital sodium (30 mg·kg⁻¹). After intubation and mechanical ventilation, under sterile technique, a modified unipolar J pacing lead (St. Jude Medical) was inserted through the right jugular vein and the distal end of the lead was positioned in the right atrium. Initial atrial capture was verified with the use of an external stimulator (DFSA, Suzhou, China). The proximal end of the pacing lead was then connected to a programmable pacemaker (made in Shanghai Fudan University, China), which was inserted into a subcutaneous pocket in the neck. The dogs in the paced group and paced + Ang-(1–7) group were paced at 500 bpm (120-ms cycle length) with the use of 0.2-ms square-wave pulses at twice-threshold current for a period of 14 days. The surface electrocardiogram (ECG) was verified after 24 h in awake dogs and then every other day to ensure continuous 1:1 atrial capture. The dogs in the sham group were instrumented without pacing and were studied 14 days after pacemaker insertion. The dogs in the paced + Ang-(1–7) group received Ang-(1–7) (6 μg·kg⁻¹·h⁻¹) intravenously by an ALZET® osmotic pump (DURECT, USA) continuously through a jugular vein catheter for 14 days during pacing. Direct systolic blood pressure was measured during anesthesia at baseline and after 14 days of atrial pacing. Surface ECG and blood pressure were recorded by a multi-channel physiological recorder (Model P48533-K, China). The Ang-(1–7) dose was selected because 6 μg·kg⁻¹·h⁻¹ is the highest dose at which the blood pressure was not affected in our preliminary study (before and 1 h after continuous Ang-(1–7) infusion the systolic blood pressures were 137 ± 13 mm Hg vs. 134 ± 15 mm Hg, P > 0.05, n = 10).

2.2. Protocol of AF induction after rapid atrial pacing

On study days, the animals were anesthetized and ventilated as above, a median sternotomy was performed. In each open chest dog, six pairs of electrodes (diameter: 1.5 mm and distance between poles: 1.5 mm) were sewn on the left and right atrial epicardia (LA and RA). The corresponding sites were at the high left and right atria (HLA and HRA), mid left and right atria (MLA and MRA), and low left and right atria (LLA and LRA). We observed the change in inducibility and duration of AF at basic pacing cycle length (BCL) of 300 (BCL300), 250 (BCL250) and 200 (BCL200) ms at 6 aforementioned sites. AF induction was defined as P wave disappearance, rapid atrial activation with irregular ventricular response on atrial ECG after atrial programmed stimulation (S1–S2). The site where AF persisted for longer than 1 s was denoted as AF induction site. The duration of induced AF was also recorded.

2.3. Histology

Small portions of the left atrial free wall were excised and fixed for histological analysis. Tissue fibrosis was evaluated by Masson's trichrome staining. Microscopic images were analyzed with Motic Images Advanced 3.2 software. Connective tissue was differentiated on the basis of its color and expressed as a percentage of the reference tissue area. These analyses were performed by a pathologist who was unaware of the treatment.

2.4. Total RNA preparation and reverse transcription-polymerase chain reaction (RT-PCR)

After the electrophysiological studies, the left atrium was cut off and used for molecular biological studies. Specimen were rapidly frozen in liquid nitrogen and stored separately at −80 °C for further analysis. One aliquot of each tissue sample was used to investigate the mRNA expression of extracellular signal-regulated kinase (ERK) 1 and ERK2. In brief, 100 mg of tissue was homogenized in 1 mL of Trizol reagent (Invitrogen, USA) extracted with chloroform and precipitated in isopropyl alcohol. Total RNA was incubated in DNase I (0.2 U/μL, Invitrogen) for 30 min, extracted by use of phenol–chloroform, precipitated in isopropyl alcohol, and subsequently dissolved in diethylpyrocarbonate-treated water. The integrity of each sample was confirmed by analysis on a denaturing agarose gel. The amount of total RNA was determined spectrophotometrically at a wavelength of 260 nm, and the RNA was stored at −80 °C for later analysis.

Specific oligonucleotide primer pairs were designed according to the sequences obtained from GenBank. The primers specific for each channel are shown in Table 1.

A 200 ng quantity of total RNA underwent RT-PCR using a commercially available kit (TaKaRa, Japan). β-Actin and GAPDH were included as control for ERK1 or ERK2, respectively. The PCR consisted of 35 cycles of 94 °C for 30 s, 51 °C (ERK1/ERK2), 52 °C (β-Actin) or 55 °C (GAPDH) for 30 s and 72 °C for 30 s. Five μL of product was analyzed by 1% agarose gel electrophoresis. Then, the resultant target gene sequence was identified by Shanghai Invitrogen Biotech Co. Ltd., Shanghai, China.

2.5. Statistical analysis

All data are expressed as mean ± SEM. Statistical comparisons among groups were performed with ANOVA. If significant effects were indicated by ANOVA, a t test with Bonferroni’s correction or Dunnett’s test was used to evaluate the significance of differences between individual mean values. Linear regression was used for correlation between the amounts of ERK1/ERK2 mRNA and atrial fibrosis in different test groups. Inducible rate of AF was analyzed with exact probability test and duration of AF was compared by Wilcoxon rank sum test. A two-tailed P < 0.05 was taken to indicate statistical significance.

3. Results

3.1. Hemodynamic parameters

As summarized in Table 2, there was no significant difference in ventricular rate or systolic blood pressure between groups at baseline (P > 0.05), and no difference was found during the pacing (P > 0.05), the heart rate and blood pressure were not changed by atrial pacing in each group (P > 0.05).

3.2. Inducibility and duration of AF

Since 6 atrial sites in each dog were used to induce AF, there were overall 36 sites of the 6 dogs in each group. Compared with the sham group, the inducible rate of AF was increased at various BCLs in the paced group (P < 0.01). Inducibility of AF was not changed by the pacing in Ang-(1–7) treated dogs compared with the sham group at various BCLs (P > 0.05). The average duration of inducible AF was shorter in Ang-(1–7) treated dogs compared to that in the paced group dogs at various BCLs (P < 0.05) (Table 3).

Table 1

<table>
<thead>
<tr>
<th>Genes</th>
<th>GenBank accession no.</th>
<th>Sense/antisense</th>
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<td>ERK1</td>
<td>DQ889350.1</td>
<td>5′-GGCGACCTCACAGTGCTTAC</td>
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<tr>
<td>ERK2</td>
<td>DQ889351.1</td>
<td>5′-GGCACCCGCTGCAGTGTGAG</td>
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<td>β-Actin</td>
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<td>GAPDH</td>
<td>NM_001003142.1</td>
<td>5′-CAACCATCCCATTCGCC</td>
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</tbody>
</table>

Lengths of amplified fragments are shown in parentheses.
3.3. Pathological examination

Representative histological sections from each group are shown in Fig. 1A–C. Interstitial fibrosis is shown in green by Masson trichrome staining. Atrial tissue from the sham dogs appeared normal. In contrast, atrial tissue from the paced group showed a large amount of interstitial fibrosis distributed throughout the tissue. In addition, heterogeneity in the size and arrangement of atrial myocytes was found in these tissues. These pathological abnormal findings were attenuated in the Ang-(1–7) group.

A quantitative analysis of fibrosis is shown in Fig. 1D. The percentage of fibrosis in the left atria in the Ang-(1–7) group was markedly lower than that in the paced group (5±1% vs. 17±1%, P<0.01), but was greater than that in the sham group (5±1% vs. 2±1%, P<0.01).

3.4. Expression of ERK1/ERK2 mRNA

Fig. 2A–B shows gels obtained by semiquantitative RT-PCR for the ERK1 and ERK2 mRNA. Lanes S, P, and A were PCR product from the sham group, paced group, or paced+Ang-(1–7) group obtained by the addition of 5 μL of the internal standard along with 5 μL of ERK1 or ERK2 PCR product, respectively. The lower band in each lane corresponds to the ERK1 (Fig. 2A) or ERK2 (Fig. 2B) mRNA product, and the upper band is the internal standard signal. Fig. 2C and D shows the mean±SEM ERK1 and ERK2 mRNA concentration in 6 hearts (1 independent determination per heart) from each group of dogs. In the paced group, ERK1 and ERK2 mRNA expression was increased significantly after 14 days of rapid atrial pacing (P<0.05 vs. sham). The observed changes in ERK1 and ERK2 mRNA concentrations paralleled changes in the interstitial fibrosis in the atria. Compared with the paced group, Ang-(1–7) prevented the increase of ERK1 (P<0.01) and ERK2 (P<0.05) mRNA expression.

There was no correlation between atrial fibrosis and ERK1 mRNA (r = 0.63, P = NS) or ERK2 mRNA (r = 0.153, P = NS) content in sham dogs. Furthermore, no linear relation between ERK1/ERK2 mRNA expression and atrial fibrosis could be demonstrated in the paced group.

### Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Heart rate (bpm)</th>
<th>Systolic blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pacing</td>
<td>Paced for 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before pacing</td>
</tr>
<tr>
<td>Sham</td>
<td>196±19</td>
<td>194±17</td>
</tr>
<tr>
<td></td>
<td>144±10</td>
<td>143±13</td>
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<tr>
<td>Paced</td>
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<td>190±19</td>
</tr>
<tr>
<td></td>
<td>141±12</td>
<td>139±10</td>
</tr>
<tr>
<td>Ang-(1–7)</td>
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<td>187±17</td>
</tr>
<tr>
<td></td>
<td>139±7</td>
<td>138±6</td>
</tr>
<tr>
<td>F</td>
<td>0.439</td>
<td>0.549</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

- F: F-test
- P: P-value

*P<0.01 vs. corresponding value in the sham group, §P<0.01 vs. corresponding value in the paced group.

### Table 3

Inducible rate and duration of atrial fibrillation at various basic pacing cycle length.

<table>
<thead>
<tr>
<th>Groups</th>
<th>BCL300 R</th>
<th>BCL300 T</th>
<th>BCL250 R</th>
<th>BCL250 T</th>
<th>BCL200 R</th>
<th>BCL200 T</th>
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<tbody>
<tr>
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<td>1/36</td>
<td>–</td>
<td>1/36</td>
<td>–</td>
</tr>
<tr>
<td>Paced</td>
<td>10/36*</td>
<td>54.1±37.8</td>
<td>11/36*</td>
<td>49.5±44</td>
<td>15/36*</td>
<td>46.1±30.9</td>
</tr>
<tr>
<td>Ang-(1–7)</td>
<td>5/36</td>
<td>5±2.6†</td>
<td>4/36</td>
<td>8±5.2†</td>
<td>4/36</td>
<td>9±4.2‡</td>
</tr>
</tbody>
</table>

AF was induced at 6 sites in each heart, six dogs and overall 36 sites were studied in each group. R, Sites where AF was induced. T, Average duration of AF (X±s, second).

*P<0.01 vs. corresponding value in the sham group, †P<0.05 vs. corresponding value in the paced group, ‡P<0.01 vs. corresponding value in the paced group.

### Fig. 1.

Panels A–C show the representative histologic sections of the left atrial free wall from a sham dog (A), non-treated paced dog (B), and Ang-(1–7)-treated dog (C). Connective tissue is shown in green. Atrial tissue from the sham dogs appeared normal. Extensive interstitial fibrosis can be seen in the paced dog, but is attenuated in the Ang-(1–7)-treated dog (×200; Masson trichrome stain). The percentage of fibrosis in the Ang-(1–7) group was lower than that in the paced group (D). S: sham group, P: paced group, A: paced+Ang-(1–7) group. *P<0.01 compared with the sham group, †P<0.01 compared with the paced group.

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4.1. ERK1/ERK2 mRNA expression changes and histological abnormalities in atrial tachycardia canine model

The opinions on the relation of left and right atria in AF remodeling were controversial. Several studies have described differences between right and left atrial changes. For example, in one study, AT1 receptors were found to be upregulated in the left and unchanged in the right atria [22]. Van Wagoner et al. [23] reported an increase in left, but not right, atrial iKs density in patients with AF. However, in some experiments, the time course and magnitude of both electrical and structural remodeling were similar between the right and left atria [21,24–27]. Therefore, we evaluated the fibrosis of the left atria and studied gene expression in the same atria to avoid the confusion of the results.

Activation of the ERK pathway by G protein-coupled receptor agonists like Ang II induces cellular differentiation processes and an activation of fibroblasts that causes the development of interstitial fibrosis [2]. Increased activation of ERK1/ERK2 provides the pathophysiologic substrate (atrial fibrosis) that predisposes to the occurrence of AF. Atrial tachycardia is a sufficient stimulus to induce the changes typical of AF-induced remodeling [28]. Nakashima and Kumagai [29] demonstrated in the atrial-pacing dogs, AERP shortening and the intra-atrial conduction times (CT) and duration of induced AF increasing were observed after 2 weeks, and continued during pacing to 4 weeks. In our study, after 14 days of atrial pacing, electrophysiological study confirmed increased AF inducibility and duration after pacing, and the increase of atrial ERK1/ERK2 mRNA expression and atrial fibrosis was identified. Based on the increase of AF vulnerability and morphological changes, 14 days of atrial pacing was sufficient to evaluate the state of atrial structural remodeling.

4.2. Effects of Ang-(1–7) on atrial fibrosis and AF vulnerability

Inhibition of Ang II pathway attenuates the formation of fibrosis and diminishes the incidence of AF [3]. In our experiment, rapid pacing for 14 days produced extensive interstitial fibrosis in the atria of the paced group, but Ang-(1–7) treatment significantly reduced the percentage of interstitial fibrosis compared with the paced group. The fibrosis can be explained to a certain extent by the expression of ERK1/ERK2. One of the mediators responsible for the development of atrial fibrosis is Ang II. Increased atrial expression of the ACE and activation of the Ang II-related intracellular signal transduction pathway have been shown in fibrillating human tissue, and the expression of ERK2 mRNA and activated ERK1/ERK2 was increased during chronic AF, amounts of activated ERK1/ERK2 were reduced in patients treated with ACE inhibitors [2]. Both ACE inhibitors and ARB can lead to regression of remodeling, restoration of normal AERPs, and AERP physiologic rate adaptation [30]. Inhibition of the ACE can reduce the generation of Ang II in CHF, which is also characterized by less atrial fibrosis and a decreased inducibility of AF [30]. AT1 receptor agonist-binding triggers phosphorylation and activating MAPK that initiates hypertrophy [2,31].

Recently, an alternative pathway of the RAS involving a homolog of ACE, termed ACE2, was discovered [12,32]. One of the properties of this carboxypeptidase is its ability to hydrolyze Ang II with high catalytic efficiency [33]. This reaction results in the generation of Ang-(1–7) [12,33]. There is evidence that ACE2 is expressed in the heart [34] and that Ang-(1–7) can be generated directly within the myocardium [35]. Additionally, overexpression of ACE2, resulted in the reversal of cardiac hypertrophy and fibrosis in rats [36]. Evidence suggested that Ang-(1–7) is a cardioprotective peptide. Ang-(1–7) and ACE2 levels are increased in hearts following myocardial infarction in rats [35,37], suggesting that ACE2 may serve as a compensatory response to cardiac remodeling. In addition, Santos et al. [38] recently identified the orphan G protein-coupled receptor Mas as an Ang-(1–7) receptor. Ang-(1–7) reduces cardiac myocytes growth.
through activation of the Mas receptor [16], suggesting that Ang-(1–7) may act as an endogenous regulator of cell growth. Thus Ang-(1–7) opposes the proliferative effects of Ang II.

Iwata et al. [14] demonstrated that Ang-(1–7) attenuates profibrotic signaling within the myocardium, through direct actions on cardiac fibroblasts. Ang-(1–7) also caused a significant reduction in serum-stimulated ERK1/ERK2 activities [16]. Tallant and Clark [39] showed that Ang-(1–7) inhibited Ang II stimulation of ERK1/ERK2 activities, whereas Ang-(1–7) itself had no effect on ERK1/ERK2 activation. Furthermore, Gallagher et al. [40] had reported that Ang-(1–7)-mediated reduction in ERK1/ERK2 activity in VSMCs was attenuated by either a tyrosine phosphatase inhibitor or a serine–threonine phosphatase inhibitor, suggesting that Ang-(1–7) reduces MAPK activity by upregulating or activating an MAPK phosphatase. Ang-(1–7) may reduce ERK1/ERK2 activity in cardiac myocytes by stimulating or inducing the expression of an MAPK phosphatase. In adult rat cardiac fibroblasts, Ang-(1–7) significantly inhibited Ang II-induced increases in gene expression of endothelin-1 (ET-1) and leukemia inhibitory factor (LIF) but not transforming growth factor-β1 (TGF-β1). These results indicated that Ang-(1–7) does not reverse gene expression of all the growth factors stimulated by Ang II but does significantly inhibit induction of some growth factors [14]. Although there was no correlation between AF duration and ERK2 mRNA content in patients with chronic AF, the amount of ERK2 mRNA was significantly increased in patients with chronic AF compared to patients with sinus rhythm [2]. Therefore, gene expression of ERK1/ERK2 is an important factor to influence the AF substrate. So in this study, we tried to provide data to show Ang-(1–7) reverses the increase of ERK1/ERK2 mRNA induced by atrial tachycardia, and our results indicated that Ang-(1–7) could inhibit the MAPK signaling at mRNA level. Ang-(1–7) reduced the pacing induced atrial fibrosis and decreased the mRNA expression of atrial ERK1/ERK2, so we postulated that the decrease of ERK gene expression is one of the mechanisms by which Ang-(1–7) prevented cardiac fibrosis. Activation of the ERK pathway alone might not be sufficient to induce the full spectrum of fibrotic changes. The simultaneous employment of various pathways may explain the no linear correlation between the expression of ERK1/ERK2 mRNA and atrial fibrosis. Furthermore, Ang-(1–7) decreased the inducibility of AF and shortened the duration of inducible AF after 14 days of atrial pacing, this effect could be attributed to the antifibrotic action of Ang-(1–7).

In a previous study by Loot et al. [41], Ang-(1–7) was infused into rats for 8 weeks after coronary artery ligation. The infusion with Ang-(1–7) improved cardiac function and was associated with a significant decrease in myocyte size. Ferrario et al. showed an upregulation of ACE2 mRNA and plasma Ang-(1–7) level by ARBs treatment of rats after myocardial infarction, the increased ACE2 mRNA correlated with elevated plasma Ang-(1–7) and reversal of cardiac remodeling [42]. These findings indicated that Ang-(1–7) potentiates the protective effects of ARBs on cardiac function and remodeling after myocardial infarction. Recently, we reported that in the atrial myocytes of chronic rapid atrial-pacing dogs, Ang-(1–7) and ARB irbesartan effectively prevented the shortening of action potential duration (APD) and the reduction of APD rate adaptation, and Ang-(1–7) suppressed the decrease of Ito and IcaL currents. Therefore, we postulated that counterbalance of the Ang II actions by Ang-(1–7) may represent an important tool to prevent atrial ionic remodeling [43].

Chronic Ang-(1–7) can prevent hypertension-induced cardiac myocyte hypertrophy and interstitial fibrosis [15]. The antifibrotic and antihypertrophic effects of Ang-(1–7) were not mediated through changes in either AT1 or Ang II type 2 (AT2) cardiac receptor numbers. Furthermore, Ang-(1–7) infusion prevented cardiac hypertrophy and fibrosis without having any effect on the elevated blood pressure induced by chronic Ang II treatment. The lack of an obvious, significant effect on blood pressure would suggest that Ang-(1–7) is likely not mediating its effects by antagonizing the AT1 receptors or ACE. These findings suggest that the beneficial effects of Ang-(1–7) are the result of direct actions on the cardiac tissue. In the present study, Ang-(1–7) treatment had no effect on blood pressure of paced dogs, but Ang-(1–7) reduced the atrial-pacing induced fibrosis. The antifibrotic effect of Ang-(1–7) is consistent with our study indicating that inhibiting structural remodeling is one of the mechanisms by which Ang-(1–7) prevented AF.

5. Limitations of the study

In this study, we did not control the ventricular rate by producing antitachycardiac (AV) node block or assess ventricular function with echocardiography. But the ventricular rate and blood pressure were not significantly changed by atrial pacing in each group, so ventricular tachycardia-induced left ventricular dysfunction might not have been caused by the pacing or have contributed to the development of atrial remodeling in this rapid atrial-pacing model. On the other hand, maintenance of physiological AV conduction is more similar to the situation of clinical cases of AF.

6. Conclusions

Our study for the first time demonstrated that, in the atria of chronic rapid atrial-pacing dogs, Ang-(1–7) prevented the atrial-pacing induced increase of ERK1/ERK2 mRNA expression and atrial fibrosis. Ang-(1–7) could effectively reduce the inducibility of AF, shortened the duration of induced AF. Hence, antifibrotic action may contribute to the beneficial effects of Ang-(1–7) on the prevention of AF.

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References


