Laboratory Research

Short-term rapid right atrial pacing induces left atrial mechanical and anatomical remodeling in a canine model

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Objective  The underlying mechanisms responsible for both electrical and mechanical remodeling of the atrium after cardioversion of atrial tachyarrhythmias may be similar, but they are still incompletely understood, and whether the changes in atrial myocardium structure after short-term rapid atrial activation is the basis for this remodeling is unknown. We aimed to investigate atrial mechanical function and atrial ultrastructural change before and after short-term rapid atrial activation, and the possible relation between left atrial contractile and anatomical remodeling. Methods  Seventeen anesthetized mongrel dogs were divided into experimental (n=12) and control (n=5) groups. The experimental group underwent insertion of a transvenous lead at the right atrial appendage and 5-hour of atrial pacing at 450bpm. Effective refractory period (ERP) and P-wave duration were measured before and after 5-hour pacing. Acoustic quantification (AQ) of left atrial waveforms was recorded before and after 5-hour pacing. All measurements were made in sinus rhythm. Dogs were killed and the myocardium in left atrial trabeculae and appendages was examined by light and electron microscopy. Control dogs did not undergo pacing, but the examinations were performed at the times corresponding to that for the experimental group. Results  Despite the absence of changes in heart rate and left ventricular pressure after 5-hour rapid atrial pacing in the experimental group, left atrial reservoir and conduit function did not change, whereas atrial size increased and atrial booster function decreased. Marked changes were seen in cellular substructures, such as loss of myofibrils, accumulation of glycogen, and changes in mitochondrial shape and size. No changes were found in the control group. Conclusions  Short-term rapid atrial activation can cause electrophysiological remodeling and left atrial contractile and anatomical remodeling, and anatomical remodeling may contribute to the development of atrial electrical and contractile remodeling (J Geriatr Cardiol 2010; 7:30-35).

Key words  fibrillation, atrial; remodeling; electrophysiology; echocardiography

Introduction

Experimental and clinical studies have confirmed that rapid atrial activation, such as during atrial fibrillation (AF) or rapid atrial pacing, may cause left atrial (LA) contractile dysfunction. However, further deterioration in atrial mechanical function after the return of normal electrical activity, LA mechanical “stunning”, 1,3 is believed to play a role in thromboembolic complications.

Why atrial contractile function deteriorates on termination of rapid atrial rates is not completely understood. Preliminary studies suggest that the atrial tissue develops structural abnormalities after long periods of AF; 4,5 however, these studies focused on chronic AF or rapid atrial pacing. Little is known about the effect of short episodes (several hours) of AF on atrial ultrastructure. In this prospective experimental study, we investigated atrial mechanical function by echocardiography, atrial ultrastructural change before and after short-term rapid atrial activation, and the possible relation between LA contractile and anatomical remodeling.

Methods

Animals  Adult mongrel dogs (n=17) were divided into experimental group (13.2±1.5 kg, n=12) and control (12.6±1.1 kg, n=5) group and anesthetized with intravenous administration of sodium pentobarbital (30 mg/kg, with additional dose of 4 mg/kg as needed). Respiration was maintained via an endotracheal tube and a mechanical ventilator. The Principle of Laboratory Animal Care published by the National Institute of Health in 1996 was followed, and the experimental protocol was approved by the Animal Care Committee of Shandong University.

Left ventricular pressure was continuously monitored by an indwelling catheter placed in the right femoral artery through a cut-down. The canine model was established with minor modification. 5 Two 6F quadripolar catheters were in-
served through a direct cut-down of the left femoral vein and were fluoroscopically advanced to the right atrial (RA) appendage and lower right atria, respectively. All data were continuously displayed on an electrophysiological recorder (RM-6000, Japanese Electronics) and recorded periodically on photographic paper at 100 and 200 mm/s, respectively. The quadripolar catheter in the RA appendage was connected to a stimulator, and that in lower right atria connected to a recorder. Experimental dogs were stimulated at 450 bpm with 4 ms pulses at twice the threshold current. Control dogs did not undergo pacing, but the examinations were performed in parallel to the experimental group.

Electrophysiological study

P-wave duration was measured from surface ECG at baseline and after pacing. The atrial effective refractory period (ERP) was measured at the lower right atria by delivering a train of 8 atrial-paced S1 at two cycle lengths (300ms and 270ms) followed by an extra-stimulus (S2) introduced at coupling intervals in decreasing intervals of 10 ms to scan the entire atrial diastolic interval. Atrial ERP was defined as the longest S1-S2 interval that failed to result in atrial depolarization.

Echo-cardiography

Experimental dogs underwent 2-D echocardiography (Hewlett Packard SONOS 5500, S8 transducer), and all dogs underwent mitral regurgitation assessment. Mitral inflow velocity was obtained by pulsed wave Doppler examination under mitral regurgitation assessment. Mitral inflow (Hewlett Packard SONOS 5500, S8 transducer), and all dogs

Hemodynamic conditions

Parameters were stable throughout the study both in the experimental group and control group. In the experimental group, the average R-R interval at baseline was similar to that after pacing (329.9±30.3 vs 317.5±26.7 ms). Mean systo...
toxic and diastolic left ventricular pressure did not differ before and after atrial pacing (109.45±11.43 vs 113.73±14.70 mmHg; 5.53±1.02 vs 6.54±1.50 mmHg, Table 1). Nonsustained AF was induced at restudy in 3 of 12 dogs in the experimental group.

**Electrophysiological findings**

In the experimental group, P-wave duration significantly increased after pacing (52.09±7.63 vs 56.09±8.62 ms, *P*<0.05); and endocardial RA ERP was significantly reduced (113.27±11.99 vs 87.27±16.35 ms, *P*<0.01, Table 1). However, compared with baseline, values did not change markedly post-rapid atrial pacing in the control group.

**Doppler echocardiography**

In the experimental group, the peak velocity of LA contraction (A) was 59.25±9.43 cm/s at baseline, and after 5-hour rapid atrial pacing, it was decreased to 48.92±10.80 cm/s (*P*<0.01). During rapid atrial pacing, we could discern no forward transmitral flow attributable to atrial contraction, and no significant difference in E, E/A, S, D and S/D before or after rapid pacing (Table 2). No dog showed mitral regurgitation.

**Acoustic quantification**

In the experimental group, after 5-hour continuous rapid atrial pacing, LAmax, Lamin, and LAoae were increased significantly (Table 3), LA AEI was increased markedly, but LA PE and LA AE did not change. All parameters were stable in the control group before and after rapid atrial activation.

**Structural changes**

Under light microscope, tissue in the control group showed normal myocytes and normal intercellular spacing in the control group before and after rapid atrial activation.

### Table 1  Hemodynamic conditions and electrophysiological findings in dogs undergoing short-term rapid pacing

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n=12)</th>
<th>Control group (n=5)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 5 hours</td>
</tr>
<tr>
<td>R-R intervals (ms)</td>
<td>329.91±30.34</td>
<td>317.45±26.73</td>
</tr>
<tr>
<td>LVESP (mmHg)</td>
<td>109.45±11.43</td>
<td>113.73±14.70</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>5.53±1.02</td>
<td>6.54±1.50</td>
</tr>
<tr>
<td>ERP (ms)</td>
<td>113.27±11.99</td>
<td>87.27±16.35*</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>52.09±7.63</td>
<td>56.09±8.62**</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P*<0.05, **P*<0.01 vs Baseline. LVESP: left ventricular end-systolic pressure; LVEDP: left ventricular end-diastolic pressure; ERP: effective refractory period.

### Table 2  Left atrial mechanical function in dogs evaluated by pulsed wave echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n=12)</th>
<th>Control group (n=5)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 5 hours</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>79.75±13.14</td>
<td>74.08±12.60</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>59.25±9.43</td>
<td>48.92±10.80**</td>
</tr>
<tr>
<td>E/A</td>
<td>1.40±0.46</td>
<td>1.59±0.52</td>
</tr>
<tr>
<td>S (cm/s)</td>
<td>62.25±9.64</td>
<td>58.17±7.69</td>
</tr>
<tr>
<td>D (cm/s)</td>
<td>46.83±7.55</td>
<td>46.17±7.26</td>
</tr>
<tr>
<td>S/D</td>
<td>1.36±0.31</td>
<td>1.29±0.27</td>
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</tbody>
</table>

Values are means ± SD. *P*<0.01 vs Baseline. E: maximal early diastolic filling velocity; A: maximal late diastolic filling velocity; S: peak forward flow velocity during ventricular systole; D: peak forward flow velocity during ventricular diastole.

### Table 3  Left atrial mechanical function evaluated by AQ in experimental and control dogs

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n=12)</th>
<th>Control group (n=5)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 5 hours</td>
</tr>
<tr>
<td>LAmax (ml)</td>
<td>5.84±1.35</td>
<td>6.19±1.11*</td>
</tr>
<tr>
<td>LAoae (ml)</td>
<td>3.26±0.90</td>
<td>3.84±0.74**</td>
</tr>
<tr>
<td>Lamin (ml)</td>
<td>1.72±0.71</td>
<td>2.30±0.54**</td>
</tr>
<tr>
<td>FA (ml)</td>
<td>4.12±0.74</td>
<td>3.89±0.75</td>
</tr>
<tr>
<td>PE (%)</td>
<td>62.52±7.34</td>
<td>59.81±11.77</td>
</tr>
<tr>
<td>AE (%)</td>
<td>37.47±7.34</td>
<td>40.19±11.77</td>
</tr>
<tr>
<td>AEI (%)</td>
<td>48.47±10.12</td>
<td>40.01±6.62*</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P*<0.05, **P*<0.01 vs Baseline. FA: filling area; PE: the passive emptying percentage of total emptying; AE: active emptying percentage of total emptying; AEI: active emptying index.
However, in the experimental group, atrial myocytes after rapid pacing were often moderately depleted of contractile material and showed mild accumulation of glycogen and fiber disarray (Fig. 2A, B).

Under electron microscope, sarcomeres, mitochondria, and intercalated disks exhibited normal microstructure in the control group (Fig. 3A), but in the experimental group, after rapid pacing, atrial myocytes showed typical alterations of a nondegenerative nature. Contractile material was depleted in some areas (myolysis). Glycogen filled the myolytic space in almost all cells undergoing myolysis. In areas depleted of sarcomeres, many mitochondria were elongated, with distinct mitochondrial swelling associated with a decreased density of the cristae, which suggested possible

**Fig. 1 Tissue from normal dog heart.** A: HE staining shows normal myocytes and normal intercellular spacing. B: PAS staining. PAS-positive material (red: glycogen) is almost absent within the myocytes. Bar = 50 μm.

**Fig. 2 Myocytes from dogs with rapid atrial activation.** A: HE staining. Myocytes show a loss of contractile elements and increased intercellular spacing. B: PAS staining. Myocytes accumulate glycogen. Bar = 50μm.

**Fig. 3 Electron microscopic examination of atrial tissue samples.** A: Atrial tissue from normal dogs. Sarcomeres, mitochondria, and intercalated disks exhibit normal microstructure. Myocyte surfaces also exhibit normal ultrastructure; B and C: sample of atrial tissue from dogs after rapid atrial pacing. Abnormal ultrastructure seen in mitochondria (swollen cristae and even enlargement, with loss of cristae definition), intercalated disk (disrupted), sarcomeres (loss of banding pattern and integrity of contractile elements) and glycogen filled the myolytic space in almost all cells undergoing myolysis. (Original magnification ×10 000)
Discussion

Assessment of LA size and function

In this study, we demonstrated brief periods of rapid right atrial pacing in normal canine hearts resulting in marked left atrial mechanical dysfunction, as evaluated by pulsed wave echocardiography and AQ.

Peak Doppler scanning velocity of mitral inflow in late diastole produced by the left atrial contraction (A-wave) was the initial Doppler scanning parameter used to evaluate LA function with transthoracic echocardiography. An A-wave velocity < 50cm/s suggests the presence of atrial mechanical dysfunction. Because of a lack of organized atrial contraction in AF, the A-wave-related parameters are not applicable during AF. Investigators have used these parameters to monitor the progressive resolution of atrial stunning. Several reports have suggested the use of pulmonary venous systolic flow as an indicator of LA reservoir function. In our study, A-wave decreased immediately after restoration to sinus rhythm, but E, S and D did not change, so short-term rapid atrial activation can affect only LA booster pump function, but not LA reservoir function.

The most commonly used non-invasive technique to evaluate LA performance is Doppler echocardiography, but the technique provides no information about LA size. AQ, an automated border detection technique, provides on-line continuous cardiac chamber area or volume over time, and can provide LA area measurements throughout the cardiac cycle. Unlike other techniques, AQ can be used to noninvasively assess LA size, as well as the reservoir, conduit, and booster pump function of the chamber.

Like the Doppler echocardiography results, LA booster pump function deteriorated significantly, with no significant change in LA reservoir function and conduit function. Although the reduced AEI reflects atrial contractile dysfunction, the reservoir function of the atria still causes significant excursions of the atrial wall.

Possible mechanism of atrial contractile remodeling

Experimental and clinical studies have shown that brief episodes of AF may cause significant impaired LA contractility. And the degree of atrial contractile dysfunction and the time for recovery are well known to highly depend on duration of the antecedent atrial fibrillation episodes. But the mechanism of atrial contractile dysfunction after conversion of AF is still incompletely understood.

The loss of atrial function is thought to be triggered by Ca overload during AF and might be mediated by decreased release of Ca from the sarcoplasmic reticulum after AF. Schotten showed that atrial contractile remodeling during several days of AF is associated with electrical remodeling and might be caused by a reduced L-type Ca current. As well the up-regulation of the sodium-calcium exchanger may increase the extrusion of calcium from the cell. Once the sinus rhythm is restored, it eliminates the calcium overload, resulting in a state of relative calcium deficiency and a paradoxical decrease in the atrial mechanical function.

Although the above mechanism may occur with short duration of AF and may persist even with AF of longer duration, our findings appear to implicate other factors in the mechanical dysfunction associated with short durations of AF.

Previously, anatomical remodeling was considered to be associated with chronic AF, which would be expected to contribute to atrial mechanical dysfunction. However, in our study, despite short episodes of rapid atrial activation, marked anatomic abnormalities appeared, possibly accounting for the decreased contractile function of the atria.

Electron microscopic examination of atrial tissue subjected to rate-induced changes revealed not only a decreased amount of myofibrils, increased glycogen, as in structural characteristics seen in fetal heart cells, but also mitochondrial swelling, as well as disorganization and possible lysis of the crista. In such cases, once the sinus rhythm is maintained, the disruption of the contractile apparatus and lack of energy supply could explain the atrial contractile dysfunction, and the process of atrial structural changes may follow a progressive course commensurate with the duration of the atrial arrhythmias.

The present study introduced a canine model of short-term rapid atrial pacing (5 hours) demonstrating atrial electrophysiological, contractile and anatomical remodeling. However, there were several limitations in our study. Longer times could be followed to identify the time needed for the return of atrial function and to determine whether any reverse structural remodeling occurs. No therapeutic strategy exists for prevention of atrial remodeling.

In conclusion, short-term rapid atrial activation (such as AF) can cause electrophysiological remodeling and left atrial contractile and anatomical remodeling, and anatomical remodeling may contribute to the development of atrial electrical and contractile remodeling.

Acknowledgements

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