Development of a Substrate of Atrial Fibrillation During Chronic Atrioventricular Block in the Goat

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Background—Atrial dilatation is an important risk factor for atrial fibrillation (AF). In the present study, we monitored the electrophysiological changes during progressive atrial dilatation in chronically instrumented goats.

Methods and Results—In 8 goats, 2 screw-in leads with piezoelectric crystals were implanted transvenously in the right atrium. After 2 weeks, atrial diameter and effective refractory period were measured. AF paroxysms were induced by burst pacing to determine the baseline AF cycle length and stability of AF. After His-bundle ablation, the above measurements were repeated once a week. After 4 weeks of complete AV block, the free wall of the right atrium was mapped and the atrium was fixed in formalin for histological analysis. After His-bundle ablation, the ventricular rate decreased from 113.8±4.8 to 44.6±2.5 bpm. Right atrial diameter increased gradually by 13.5±3.9% during 4 weeks of AV block (P<0.01). The duration of induced AF paroxysms increased from 4.6 seconds to 6.4 minutes (P<0.05). Atrial effective refractory period and AF cycle length remained constant. Spontaneous paroxysms of AF were not observed. Atrial mapping during rapid pacing revealed that slow conduction (<30 cm/s) was present in 3.7±1.0% of the mapped area (control, 0.9±0.5%, P<0.05). Histological analysis showed hypertrophy without atrial fibrosis. Connexin40 and connexin43 expression was unchanged.

Conclusions—Chronic AV block in the goat leads to progressive atrial dilatation, prolongation of induced AF paroxysms, and local conduction delays. The increase in AF stability was not a result of a shortening of atrial refractoriness or atrial fibrosis. (Circulation. 2005;111:30-37.)

Key Words: electrophysiology | atrium | fibrillation | dilatation | mapping

Large prospective clinical trials have shown that chronic atrial dilatation is an important and independent risk factor for the development of atrial fibrillation.1 Furthermore, spontaneous conversion of AF to sinus rhythm is less likely to occur in enlarged atria.2 However, the mechanisms by which atrial dilatation creates a substrate for AF are largely unknown. First, an increase in atrial surface per se may allow more reentrant circuits to coexist. Second, a shortening of the wavelength because of a shortening of the atrial effective refractory period (AERP) and/or a reduced conduction velocity (CV) would augment the number of waves that can be present simultaneously. Third, inhomogeneities in atrial refractoriness or conduction could stabilize the arrhythmia. Finally, stretch-induced focal activity could induce or perpetuate AF in dilated atria.

In the present study, we used a goat model of chronic complete AV block to produce progressive dilatation of the atria. Chronic endocardial instrumentation made it possible for us to follow the time course of atrial dilatation and the associated electrophysiological changes. The development of a substrate of AF was monitored by measurement of the duration of electrically induced paroxysms of AF.
Electrophysiological Measurements

AERP was measured at pacing intervals of 400, 300, and 200 ms at the anterolateral wall of the RA. Single premature stimuli (4× threshold) were interpolated after every fifth interval, starting at a coupling interval shorter than the AERP. The longest coupling interval (steps of 2 ms) not resulting in a propagated response was taken as the AERP. The first propagated response was used to test the inducibility of AF (1 second). AF stability was expressed as the mean duration of AF paroxysms repetitively induced by burst pacing (50 Hz; 1 second; 4× threshold) during 1 hour. If a single episode lasted >1 hour, the measurement was terminated. Median AF cycle length (AFCL) was determined from 100 consecutive AF intervals.

After 4 weeks of AV block, the animals were anesthetized again (thiopental 10 to 15 mg/kg IV, halothane 1%, and a 1:2 mixture of O₂ and N₂O), and the heart was exposed by a left thoracotomy. Spatial dispersion of atrial refractoriness was determined by measuring the AERP (pacing interval, 350 ms) at 9 different sites, both at the free wall of the RA and LA and at Bachmann’s bundle. To analyze atrial conduction, a spoon-shaped mapping electrode (diameter, 4 cm; 234 unipolar electrodes; interelectrode spacing, 2.4 mm) was placed on the RA free wall. To measure atrial conduction during sinus rhythm and atrial pacing (400, 300, and 200 ms), maps from 5 consecutive beats were analyzed. A curved arrow was drawn manually normal to uniformly spaced isochrones across the mapping area. From the length of this arrow and the number of isochrones, the effective uniform CV along that path was obtained (Figure 2). Regions of nonuniform or delayed conduction were excluded. With a second method, local conduction vectors were calculated in areas of 2×2 electrodes, as described by Holm et al.4 This method included local conduction delays and was used to measure spatial heterogeneities in conduction.5,6 Analysis of 5 consecutive beats resulted in a total of approximately 1000 local conduction vectors. Although the individual vectors showed considerable variation, the histogram of the length of these vectors provided a reliable measurement of local CV. For comparison with previous studies, the distribution of local conduction times (difference in activation time between neighboring electrodes) and phase differences (maximal time difference in areas of 2×2 electrodes) were also measured. The heterogeneity index was expressed as the 95th percentile minus the 5th percentile of the phase difference distribution (p95–p5) divided by the median phase difference (p50).7

Histology

The hearts were fixed in buffered formalin, and samples from the upper and lower free wall of the RA and LA (trabeculated area) were embedded in paraffin. Sections 4 μm thick were stained with Sirius red (collagen) or a modified azan technique (myocytes). The relative collagen content was determined excluding pericardial, endocardial, and perivascular fibrosis.8 The size of atrial myocytes was measured in cells showing a nucleus in the center and intercalated disks on
### Hemodynamic Characteristics, Atrial Size, and Conduction

<table>
<thead>
<tr>
<th></th>
<th>Sinus Rhythm</th>
<th>Acute AV Block</th>
<th>4 Weeks AV Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial rate, bpm</td>
<td>113.8±4.8</td>
<td>129.5±7.7</td>
<td>106.8±4.7†</td>
</tr>
<tr>
<td>Ventricular rate, bpm</td>
<td>113.8±4.8</td>
<td>44.6±2.5†</td>
<td>53.5±2.7†</td>
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<td>Cardiac output, L/min</td>
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<td>2.34±0.54†</td>
<td>2.74±0.27*</td>
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<td>Stroke volume, mL</td>
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<td>50.4±10.0</td>
<td>52.2±6.1</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>147.4±6.1</td>
<td>120.0±11.7</td>
<td>136.8±13.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>119.0±5.3</td>
<td>78.5±8.2†</td>
<td>93.4±9.4</td>
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<td>RAP, mm Hg</td>
<td>4.3±0.6</td>
<td>10.1±2.1†</td>
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<td>PCWP, mm Hg</td>
<td>5.7±1.3</td>
<td>9.3±1.8</td>
<td>11.1±0.8*</td>
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<td>LVEDP, mm Hg</td>
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<td>14.2±1.7†</td>
<td>12.5±1.2*</td>
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<td>RA diameter, mm</td>
<td>27.8±4.6</td>
<td>26.6±4.4</td>
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<td>LA dimensions, mm</td>
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<td>Anteroposterior</td>
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<td>62.3±2.9*</td>
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<td>84±2</td>
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<td>106±7*</td>
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<tr>
<td>LA</td>
<td>92±2</td>
<td>...</td>
<td>116±7*</td>
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<tr>
<td>Myocyte width, μm</td>
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<tr>
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<td>13.0±0.9</td>
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<td>16.6±1.3</td>
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<td>97±3</td>
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<td>108±4</td>
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<td>96±3</td>
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<tr>
<td>Local CV &lt;30 cm/s, %</td>
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<tr>
<td>SR</td>
<td>0.5±0.3</td>
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<td>0.5±0.3</td>
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<tr>
<td>Pacing 400 ms</td>
<td>0.5±0.2</td>
<td>...</td>
<td>1.0±0.4</td>
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<tr>
<td>Pacing 300 ms</td>
<td>0.7±0.4</td>
<td>...</td>
<td>1.4±0.6</td>
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<tr>
<td>Pacing 200 ms</td>
<td>0.9±0.5</td>
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<td>3.7±1.0*</td>
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<td>CT &gt;8 ms, %</td>
<td>0.6±0.3</td>
<td>...</td>
<td>2.0±0.5*</td>
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<td>Phase differences &gt;8 ms, %</td>
<td>3.0±0.8</td>
<td>(P=0.05)</td>
<td>8.0±2.2</td>
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<td>P state, ms/mm</td>
<td>0.67±0.21</td>
<td>(P=0.55)</td>
<td>0.83±0.17</td>
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<td>P state, ms/mm</td>
<td>1.18±0.07</td>
<td>(P=0.60)</td>
<td>1.25±0.11</td>
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<td>6.50±0.56</td>
<td>(P=0.07)</td>
<td>8.67±0.88</td>
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<tr>
<td>Heterogeneity index (Pstate/Pio)</td>
<td>2.43±0.23</td>
<td>(P=0.06)</td>
<td>3.26±0.31</td>
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</table>

*RAP indicates mean right atrial pressure; PCWP, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; CV, conduction velocity RA free wall; and CT, conduction times during pacing at 200 ms. Phase differences and heterogeneity index during pacing at 200 ms interval. Values are mean±SEM (No. of animals, see Methods).

### Results

#### Hemodynamic and Neurohumoral Changes Caused by AV Block

During 4 weeks of AV block, the body weight of the instrumented goats did not change (53.1±5.3 versus 51.3±2.9 kg). The heart weight/body weight ratio was higher in the atrioventricular (AV)-block group (6.9±0.5 versus 5.5±0.2 g/kg, P<0.05). The idioventricular rhythm (44.6±2.5 bpm, Table) did not change significantly during the 4 weeks of AV block. The atrial rate initially increased from 114±5 to 130±8 bpm and returned to baseline values within 4 weeks (107±5 bpm). Hemodynamic measurements showed an increase in stroke volume by approximately 40% (Table). Cardiac output decreased acutely from 4.1±0.2 to 2.3±0.5 L/min and was slightly improved after 4 weeks of AV block (2.7±0.3 L/min). During idioventricular rhythm, both systolic and diastolic blood pressure were lower than during sinus rhythm. Left ventricular end-diastolic pressure increased acutely by 6.5 mm Hg. Also, the mean in RA and pulmonary wedge pressure increased after His-bundle ablation. These pressures did not rise further during 4 weeks of AV block, indicating that the animals did not develop progressive heart failure.

Figure 3 shows heart rate and plasma levels of neurohormones. Within the first week of AV block, norepinephrine, atrial natriuretic factor, angiotensin II, and aldosterone increased approximately 3-fold. During 4 weeks of follow-up, none of these neurohormones increased further. The plasma levels of norepinephrine and aldosterone tended to decrease again.

#### Atrial Dilatation and Duration of AF

In Figure 4, the changes in RA diameter and duration of electrically induced AF paroxysms during the first 4 weeks of AV block are plotted for all goats. In the first week after His-bundle ablation, RA diameter decreased slightly. Thereafter, atrial size increased progressively from 27.8±4.6 to 31.6±5.5 mm after 4 weeks of AV block (+13.5±3.9%; P<0.0001). In 1 goat (Δ), the RA was still not dilated after 4 weeks of idioventricular rhythm. In 2 others (O and □), the atria started to dilate only in the third week after AV block. In these goats (Δ-O-□), the duration of AF paroxysms remained short. In animals with marked dilatation, AF duration became prolonged to more than 1 hour. In general, the increase in atrial size was accompanied by an increase in duration of AF (correlation coefficient, r=0.53; P<0.001). The low correlation coefficient was primarily because of the high interindividual variation (lower panels). The inducibility of AF did not change significantly during 4 weeks of AV block (10.7±7.4% versus 4.6±2.4%, P=0.32).

To determine whether the left atrium dilated to the same extent as the right atrium, in a separate series of 6 control and 5 AV-block goats, the dimensions of the RA and LA free
walls were measured directly after excision of the heart. After 4 weeks of AV block, the anteroposterior dimension of the RA and LA had increased by 24% and 29% ($P<0.01$) and the craniocaudal dimension by 32% and 25% ($P<0.001$ and $P<0.01$; for absolute values, see Table). The surface of the right and left atrial walls was enlarged by 64% and 58% ($P<0.001$ and $P<0.01$). There was no difference between the degree of RA and LA enlargement ($P=0.75$).

**Atrial Refractoriness**

Figure 5 shows the AERP (pacing intervals of 400, 300, and 200 ms, RA) and AFCL before and after His-bundle ablation.
During 4 weeks of slow idioventricular rhythm, the AERP remained constant. Also, the differences between AERP400, AERP300, and AERP200, representing the physiological rate adaptation, remained the same. Before His-bundle ablation, the median AFCL was 152/1006 10 ms, compared with 132/1006 6 ms after 1 week and 139/1006 11 ms after 4 weeks of AV block (P = 0.51). After 4 weeks of idioventricular rhythm, the goats (n=7) were anesthetized and the AERP was measured at 9 epicardial sites. The coefficient of spatial variation and the maximal spatial difference in AERP were lower than in the control group (0.14/1006 0.01 versus 0.27/1006 0.04, P = 0.01, and 49/1006 6 versus 78/1006 5 ms, P = 0.01). This indicates that the increase in stability of AF after 4 weeks of AV block was not a result of a higher dispersion in the refractory period.

**Mapping of Atrial Conduction**

The effective CV in the RA wall during sinus rhythm and slow atrial pacing (400 ms) was slightly increased in AV-block goats versus control animals (108/1006 4 versus 97/1006 3 cm/s, P = 0.06, and 108±4 versus 92±3 cm/s, P < 0.05). Also, during rapid pacing (300 to 200 ms), atrial CV was similar in both groups (97±2 versus 93±4, P = 0.41, and 96±3 versus 92±3 cm/s, P = 0.35; Figure 6, top). The percentage of areas with slow conduction (CV < 30 cm/s) was not different in the 2 groups both during sinus rhythm (0.50±0.26% versus 0.50±0.30%; P = 1.0) and during pacing at 400 ms (0.97±0.44% versus 0.53±0.25%, P = 0.41) and 300 ms (1.54±0.63 versus 0.67±0.39%, P = 0.37). However, during rapid pacing (200 ms), more areas of slow conduction were seen after 4 weeks of AV block (3.67/1006 1.03% versus 0.88/1006 0.46%, P < 0.05; Figure 6, bottom). Similarly, the incidence of long local conduction times (>8 ms) and phase differences (>8 ms) was increased during rapid pacing in dilated atria (Table; P = 0.05). Also, the heterogeneity index calculated from the phase histograms tended to be higher.

**Histological Changes**

In AV-block goats (n=9), a marked hypertrophy of cardiomyocytes was observed in the free wall of both atria (RA: cell length, +26% [P < 0.05]; cell width, +26% [P = 0.05], LA: cell length, +26% [P < 0.05]; cell width, +26% [P = 0.06]; Figure 7; absolute values in Table). The relative tissue area positive for collagen was significantly lower after 4 weeks of AV block (RA: 9.5/1006 0.7% versus 13.7/1006 1%, P = 0.01; LA:...

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**Figure 3.** Heart rate and plasma levels of norepinephrine (noradrenaline), atrial natriuretic factor (ANF), angiotensin II, and aldosterone before and during first 4 weeks of AV block. *P* < 0.05.

**Figure 4.** Top, Time course of relative changes in atrial size and duration of induced AF paroxysms during 4 weeks of AV block (8 goats). One goat (*) was euthanized at day 15 because of sepsis (†). Bottom, Individual correlation between atrial size and AF duration for some goats. Overall, correlation coefficient within subjects is 0.53, *P* < 0.001.

**Figure 5.** RA refractory period and median AFCL of 8 chronically instrumented goats during first 4 weeks of complete AV block. Neither AERP nor AFCL changed over time.
6.5±0.7% versus 10.7±1%, *P* < 0.01). This suggests that the absolute amount of collagen remained the same, whereas the myocytes became enlarged. No atrial fibrosis or signs of degeneration of myocytes were seen after 4 weeks of AV block. Immunohistochemistry of the RA and LA showed that Cx40 and Cx43 remained expressed predominantly at the end-to-end connections of the myocytes. Also, the intensity of Cx40 and Cx43 staining was similar in control and AV-block animals. In general, Cx40 was expressed more heterogeneously than Cx43, but this was true in both control and AV-block animals (Figure 7).

**Discussion**

Chronic complete AV block and the resulting slow idioventricular rhythm cause volume overload and ventricular hypertrophy. In the present study, we showed that it also leads to progressive atrial enlargement. Although the mean atrial pressures rose abruptly after His-bundle ablation, the atria became enlarged only after 1 week. This can be explained by the fact that during slow idioventricular rhythm, the ventricular systole, during which atrial size is largest, composes a shorter period of the cardiac cycle (Figure 1). The pericardium may also initially prevent atrial dilatation.11 During chronic volume overload, the pericardial sac gradually enlarges, thereby allowing the atria to dilate.12 We could not follow the changes in left atrial size because, owing to the anatomy of the caprine chest, this is not possible echocardiographically. However, after 4 weeks of AV block, the pressure was equally increased in both atria, as were the surface area of the free wall and the cell size. As in the dog model of chronic AV block,13 left ventricular end-diastolic pressure and cardiac output changed acutely but remained constant during the 4 weeks thereafter (no signs of heart failure). Atrial sinus rate showed a transient increase. The

**Figure 6.** Isochrone maps of RA free wall during rapid pacing (interval, 200 ms) in control and after 4 weeks of AV block. Effective CV was similar in both cases (97 and 100 cm/s). Histogram shows increased frequency of apparently slow local CVs after 4 weeks of AV block.

**Figure 7.** Photomicrographs from sections of RA. A modified azan staining was used to determine cell size, and Sirius red was used to visualize collagen. After 4 weeks of AV block, atrial myocytes were clearly enlarged, whereas collagen was not increased. Immunohistochemistry with antibodies against Cx40 and Cx43 showed expression of gap junction proteins.
plasma levels of several neurohormones increased and either reached a new steady state or gradually returned toward their original values. The atrial myocytes became markedly enlarged, but no signs of atrial fibrosis were seen. Four weeks of AV block and slow idioventricular rhythm thus create a different substrate of AF than heart failure or valvular dysfunction.\textsuperscript{14–18}

**How Does Atrial Dilatation Promote AF?**

Atrial dilatation may cause atrial ectopy, which triggers paroxysms of AF. In isolated guinea pig hearts, an acute increase in atrial volume induced premature beats and atrial arrhythmias.\textsuperscript{19} Dogs with mitral valve fibrosis and LA enlargement also exhibited atrial arrhythmias.\textsuperscript{18} In our present study, spontaneous atrial premature beats or paroxysms of AF were never observed. All episodes of AF were induced by electrical stimulation.

Apart from providing a trigger, atrial dilatation may also create a substrate of AF. The underlying mechanisms could include rapid foci, an increase in atrial size, together with a short wavelength and an increase in spatial heterogeneity in AERP or conduction. Studies addressing the acute mechanoelectrical feedback on AERP show contradictory results.\textsuperscript{19–25} Few studies have been performed on the electrophysiological effects of chronic atrial dilatation. In patients requiring permanent pacing, Sparks et al\textsuperscript{20} found that compared with DDD pacing, after 3 months of VVI pacing, the atria were enlarged and the AERP was prolonged. The first animal studies were performed in the early 1980s by Boyden and Hoffman.\textsuperscript{21} In 8 dogs with tricuspid regurgitation and LA enlargement also exhibited atrial arrhythmias.\textsuperscript{18} In our present study, spontaneous atrial premature beats or paroxysms of AF were never observed. All episodes of AF were induced by electrical stimulation.

In our present study, there was a tendency for the atrial refractory period to shorten during the first week after His-bundle ablation. However, at this time, the atria were not yet dilated, and the paroxysms of AF were still of short duration. When the atria started to dilate and AF became more persistent, atrial refractoriness remained constant, and the physiological rate adaptation was also preserved. After 4 weeks of AV block, the spatial dispersion of AERP was less than during control. Therefore, changes in AERP did not seem to play a major role in the development of atrial fibrillation.

Experimental studies have shown that acute atrial stretch prolongs the conduction time between 2 anatomic landmarks and increases spatial heterogeneities in conduction.\textsuperscript{6,22,24} In a canine model of progressive heart failure, interstitial fibrosis and heterogeneous conduction were considered important determinants of the substrate for AF.\textsuperscript{14} In human studies as well, atrial dilatation and impaired conduction were correlated with atrial arrhythmias.\textsuperscript{27–29} A reduced CV shortens the wavelength and thereby could stabilize AF. In our present study, the uniform CV in the dilated RA was slightly increased, possibly because of an increase in atrial cell size.\textsuperscript{30} During rapid pacing, no effect on uniform CV was found, but the incidence of local conduction delays was clearly higher after 4 weeks of AV block. This increased spatial heterogeneity in conduction may support the perpetuation of AF.\textsuperscript{7} Interestingly, interstitial fibrosis was not seen in the present model. Also, the expression of Cx40 and Cx43 was unchanged. A decrease in cell-to-cell coupling therefore does not seem to be involved in the observed conduction disturbances. According to Laplace’s law, an increase in atrial pressure and diameter will increase atrial wall stress. As a result, particularly the thinner parts of the atrial wall will be stretched.\textsuperscript{21} In isolated cardiac muscle strips, it has been demonstrated that at a certain critical level, stretch depresses conduction.\textsuperscript{6,21,31} In the isolated rabbit heart, acute atrial dilatation slowed atrial conduction and caused spatial heterogeneities.\textsuperscript{9} The atrial architecture leading to spatial differences in wall stress may explain the heterogeneities in conduction observed during atrial enlargement.

**Limitations and Clinical Implications**

This study does not prove a causal relationship between chronic atrial dilatation and increased stability of AF. The correlation between dilatation and AF duration was rather weak ($r=0.53$), indicating that other factors are also involved and that dilatation may be an epiphenomenon. The degree of atrial dilatation measured in vivo was limited (13.5%), whereas postmortem analysis revealed a more pronounced increase in atrial size (25% to 30%). Although it is difficult to judge which method is more reliable, the degree of atrial dilatation was moderate at most. Another limitation of our study is that atrial dilatation resulting from chronic AV block does not have a clinical counterpart, because the slow idioventricular rhythm is prevented effectively by pacemaker therapy. The main goal of our study was to create an experimental model of progressive atrial dilatation without concomitant heart failure.

A chronically increased atrial pressure dilated the atria slowly but steadily. After 4 weeks, the effects on atrial electrophysiology were still minor and did not lead to spontaneous or persistent AF. However, induced paroxysms of atrial fibrillation became longer in duration and in some cases lasted more than 1 hour. Studies in humans have shown that even a limited increase in atrial size (LA diameter, 40 to 50 mm) is associated with an increased risk of AF.\textsuperscript{1} Our results suggest that this higher propensity of AF is because of increased heterogeneities in conduction. Considering our model as an early stage in the development of AF, a more prolonged rise in atrial pressure may lead to more extensive dilatation and more severe atrial conduction defects. The slow nature of the changes observed in our experiments is in agreement with the slow time course of the development of AF (often years) observed clinically. Measures to prevent the development of atrial dilatation in patients may help to delay the development of an electrophathological substrate of AF.

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