Left atrial systolic and diastolic function accompanying chronic rapid pacing-induced atrial failure

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Hoit, Brian D., Yanfu Shao, and Marjorie Gabel. Left atrial systolic and diastolic function accompanying chronic rapid pacing-induced atrial failure. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H183–H189, 1998.—The objective of this study was to examine the hypothesis that long-term, rapid atrial pacing produces a model of atrial systolic and diastolic dysfunction but does not alter ventricular function. Eight dogs were atrially paced at 400 beats/min (3:1–5:1 ventricular response) for 6 wk and subsequently instrumented with left atrial (LA) and left ventricular (LV) sonomicrometers and micromanometers. Data were compared with those from six sham-operated controls at matched heart rates and mean LA pressures of 10 mmHg. Dogs with rapid pacing had slightly greater LA volume (10.3 ± 4.0 vs. 7.9 ± 4.4 mL) and reduced ejection fraction (2.2 ± 1.4 vs. 13.0 ± 4.0, P < 0.05), systolic ejection rate (0.3 ± 0.1 vs. 2.8 ± 1.2 vol/s, P < 0.05), and reservoir fraction (0.07 ± 0.04 vs. 0.35 ± 0.06, P < 0.05) compared with controls. LA diastolic chamber stiffness was greater after rapid atrial pacing than before (stiffness constant k<sub>s</sub>, 5.7 ± 2.3 vs. 3.4 ± 0.6, P < 0.05), and the ratio of transesophageal echo-determined pulmonary venous systolic to diastolic integrated flow (a measure of relative reservoir to conduit function of the LA) was less in rapidly paced dogs compared with control dogs (0.41 ± 0.19 vs. 0.68 ± 0.23, P < 0.05). In contrast, rapid atrial pacing did not influence LV systolic performance or lusitropy, because the LV pressure time derivative and the time constant of LV relaxation were similar in both groups. In this model of isolated atrial myopathy, increased atrial stiffness and enhanced conduit function compensate for impaired atrial booster pump and reservoir functions.

EXPERIMENTAL MODELS of both sustained (e.g., 6 wk) and short-term paroxysmal (e.g., 5 and 30 min) atrial fibrillation induced by rapid pacing (>400 beats/min) have been shown to result in impaired atrial contractility (16, 17, 19). Although we recently demonstrated that after 1 wk of rapid atrial pacing, noninvasively determined indexes of atrial booster pump function were markedly impaired (9), the more chronic effects of atrial tachyarrhythmia on invasively and noninvasively determined measures of atrial systolic and diastolic function are unknown. This gap in our knowledge is particularly relevant insofar as chronic rapid atrial pacing is a potentially important model for the study of both the electrophysiological and mechanical consequences of atrial arrhythmias. For example, the model has been used to demonstrate atrial remodeling and sinus node dysfunction owing to chronic atrial fibrillation (4, 9, 19). Moreover, largely for methodological reasons, the contributions of atrial function toward cardiovascular performance and ventricular filling remain controversial (2, 7, 23). Thus the objective of the current study was to examine the hypothesis that long-term (6 wk), rapid (400 beats/min) atrial pacing myopathy produces a model of isolated atrial myopathy characterized by impaired atrial systolic and diastolic function and unaltered ventricular function.

METHODS

Fourteen conditioned mongrel dogs were used in these experiments. Eight dogs weighing 21–25 kg (23.7 ± 1.7 kg) were studied 6 wk after rapid (400 beats/min) atrial pacing. Six dogs weighing 19–25 kg (22.8 ± 2.4 kg) were instrumented with a right atrial pacemaker (see below) but were un-paced; these sham-operated dogs served as controls. Animals were anesthetized with pentobarbital sodium (30 mg/kg iv). A unipolar pacemaker (Medtronic; Bloomington, MN) lead was sutured to the right atrial appendage through a right lateral thoracotomy and small pericardiotomy. In eight dogs, a pulse generator programmed at 400 beats/min was implanted in the subcutaneous tissue over the back of the neck. Six weeks after we instituted rapid pacing, the pacemaker was reprogrammed to 30 beats/min, and the animals underwent hemodynamic study. The remaining six dogs had the pacing lead and pulse generator (set at 30 beats/min) implanted and served as controls. Sham dogs were studied after a minimum of 2 wk after surgery. Long-acting diltiazem (Cardizem 300 mg) was given daily to slow the ventricular response (3:1 to 5:1) in all animals.

Hemodynamic studies were performed as described previously (14). Briefly, animals were anesthetized with pentobarbital sodium (30 mg/kg) and morphine sulfate (3 mg/kg sc) and then intubated and ventilated with a positive-pressure respirator (Harvard Apparatus, South Natick, MA). The heart was exposed with a left lateral thoracotomy at the fourth intercostal space and was suspended in a pericardial cradle. A 7-Fr micromanometer with lumen (Millar Instruments, Houston, TX) was advanced into the left atrium via a pulmonary vein; a second 7-Fr micromanometer with lumen (Millar Instruments) was advanced into the left ventricle through an apical stab wound. A femoral vein was cannulated to administer intravenous fluids. An 8-Fr catheter with a 10-ml capacity balloon was advanced from the femoral vein into the inferior vena cava just below the right atrium, and a second balloon catheter was advanced from the jugular vein into the superior vena cava.

Pairs of 3-MHz sonomicrometers (6-mm diameter, Triton Technology, San Diego, CA) were sewn to the epicardial anterior and posterior walls (long axis) of the left atrium as previously described (11, 14, 15). A pair of 3-MHz (7-mm diameter) sonomicrometers were sewn to the anterior and posterior left ventricular epicardium to measure the minor axis dimension. The transit time of ultrasound between each crystal pair was measured with a multichannel sonomicrometer (Triton Technology).

The pressure waveforms from the micromanometers were matched with those of the fluid-filled catheters. Analog
signals for left ventricular (LV) and left atrial (LA) pressures and atrial dimensions were digitized through an analog-to
digital board (Data Translation, Marlboro, MA) interfaced to
an IBM AT computer with a 2-ms sampling frequency and were stored on floppy disk.

Fluid-filled catheters were connected to Statham 23 dB pressure transducers with zero pressure set at the level of the
mid right atrium. The electrocardiogram and analog signals for pressures and dimensions were recorded on-line at slow
and rapid paper speeds (5, 25, and 100 mm/s) on a multichannel
physiological recorder (Gould, Cleveland, OH).

A Hewlett-Packard biplane transesophageal imaging trans-
ducer was lubricated and advanced into the esophagus be-
hind the atrium. The left upper pulmonary vein and mitral
valve were visualized in transverse and orthogonal longitudi-
nal views. Color flow-directed Doppler identification of intra-
cavity flow was used in all instances. Transmitial flow was
obtained from apical four-chamber and orthogonal two-
chamber views with the sample volume placed within the left
ventricle between the opened mitral leaflet tips. Pulmonary
venous flow velocity was sampled from a left superior pulmo-

nary vein, 1–2 cm proximal to the left atrium. Attempts were
made to maintain the angle between the ultrasound beam
and various flows within 30°.

Experiments were conducted in accordance with institu-
tional guidelines and the Guide for the Care and Use of
Laboratory Animals put forth by the United States Depart-
ment of Health and Human Services. The experimental
protocol was approved by the Institutional Animal Care and
Use Committee at the University of Cincinnati.

Experimental Protocols

Hemodynamic studies. The heart rate was slowed with
10–20 mg DKAH 0264 (Boehringer Ingelheim), an agent that
inhibits the sinoatrial (SA) node, current without effects on
myocardial contractility (8). Constant heart rate was achieved
by right atrial pacing with the pacing rate selected to
eliminate competing rhythms and to permit separation of
active from passive atrial emptying. Atrioventricular (AV)
conduction, measured from the onset of the atrial pacing
wave to that of the ventricular QRS, remained active from passive
atrial emptying. Atrioventricular (AV) sequential pacemaker set at 72 beats/min with an AV
interval of 200 ms (Medtronic, Minneapolis, MN) in
the manner described for the larger study.

Postmortem Studies

At the end of the experiment, animals were euthanized with a pentobarbital sodium overdose (65 mg/kg iv). The hearts were immediately removed, divided into right and left
atria and right and left ventricles, and weighed on a balance
(Galaxy 400, Ohaus, Florham Park, NJ).

Data Analysis

LA variables. The LA dimension signals were analyzed as
previously described (11, 14, 15). Maximum LA dimension
(LAmax) was taken as the largest atrial dimension corre-
sponding to the V wave on the LA pressure tracing, LA end-diastolic
dimension (LAed) was taken as the largest diameter immedi-
ately preceding the A wave of the LA pressure tracing, and LA
end systolic (LAes) was taken as the smallest dimension at the
end of LA contraction. Relative LA volume was estimated as a
general ellipsoid of revolution (14): LA volume = (π/6)(SAX)3 ·(LAX), where SAX is the short or mediolateral axis,
and LAX is the long or anteroposterior axis of the left atrium.

LA stroke volume was calculated as LA end-diastolic
volume minus end-systolic volume. LA ejection fraction was


<table>
<thead>
<tr>
<th>n</th>
<th>HR, beats/min</th>
<th>LAP, mmHg</th>
<th>LVSP, mmHg</th>
<th>LV dP/dt, mmHg/ml</th>
<th>LVFS, %</th>
<th>τ, ms</th>
<th>LV Stiffness Constant, mmHg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMYO</td>
<td>8</td>
<td>98 ± 7</td>
<td>10.5 ± 0.8</td>
<td>100 ± 9</td>
<td>1,353 ± 207</td>
<td>7.4 ± 2.4</td>
<td>43.2 ± 3.2</td>
</tr>
<tr>
<td>Sham</td>
<td>6</td>
<td>96 ± 7</td>
<td>10.2 ± 2.1</td>
<td>112 ± 10</td>
<td>1,547 ± 203</td>
<td>7.7 ± 2.3</td>
<td>41.4 ± 5.9</td>
</tr>
</tbody>
</table>

Data are means ± SD; n = no. of dogs. AMYO, atrial myopathy; HR, heart rate; LAP, LA pressure; LVSP, left ventricular (LV) systolic
pressure; LV dP/dt, peak rate of rise of isovolumetric LVSP; LVFS, LV shortening fraction; τ, time constant of isovolumic relaxation. *P < 0.05
vs. sham.
The atrial diastolic dynamic chamber stiffness constant (k) (modulus of chamber stiffness) was determined by fitting LA pressure-volume data at LAmax to the exponential curve equation, $P = A e^{V}$ (Delta Graph, Deltapoint, Monterey, CA), where P is LA pressure, the constant A is the y intercept, e is the base of the natural logarithm, and V is LA volume. A range of atrial pressure and volume was derived from either phenylephrine boluses or vena caval occlusion. To normalize the range of atrial pressure and volume was derived from either the base of the natural logarithm, and V is LA volume. A

Atrial stiffness constants were also calculated using an offset term $P_o$; thus $P(1 + k/V)$, where $P(1 + k/V)$ = $P_o$ (18). Atrial stiffness constants were also calculated using an offset term $P_o$; thus $P(1 + k/V)$, where $P(1 + k/V)$ = $P_o$ (18). Atrial stiffness constants were also calculated using an offset term $P_o$; thus $P(1 + k/V)$, where $P(1 + k/V)$ = $P_o$ (18). Atrial stiffness constants were also calculated using an offset term $P_o$; thus $P(1 + k/V)$, where $P(1 + k/V)$ = $P_o$ (18). Atrial stiffness constants were also calculated using an offset term $P_o$; thus $P(1 + k/V)$, where $P(1 + k/V)$ = $P_o$ (18).

In addition to booster pump function, the left atrium serves as a reservoir for LV filling during ventricular systole. Therefore, the increase in LA volume from minimum (at the time of mitral valve closure) to maximum (at the time of mitral valve opening) represents the reservoir volume of the atrium (6). The LA reservoir function was assessed by the reservoir volume fraction at a matched LAP of 10 mmHg; $k_c$, atrial stiffness constants calculated with a pressure offset; $k_c$, normalized stiffness constant. *P < 0.05 vs. sham.

LV variables. The time constant of LV relaxation was derived from the high-fidelity LV pressure tracing using the method of Weis et al. (26). Data from five end-expiratory beats were digitized by hand (Sigma Plot) and averaged. LV dP/dt was obtained by electronic differentiation of the high-fidelity LV pressure signal. LV end-diastolic (LVEDD) and end-systolic (LVESD) dimensions were taken as the maximum and minimum LV external sonomicrometer dimensions, respectively. LV fractional shortening (LVFS) was defined as $[(LVEDD - LVESD)/LVEDD]$. LV volume was estimated from the LV epicardial sonomicrometer diameter (D) as volume = $(D^3/6)$. LV diastolic chamber compliance was estimated by fitting end-diastolic LV pressure and volume data to the exponential curve equation, $P = A e^{V}$.

Echocardiography. Diastolic transmitral waveforms were analyzed for the peak and integral early (E) and late (A) velocities and their ratios (E/A); owing to the relatively slow heart rates, the early and late waveforms did not overlap. Fractional early (EFr) and fractional late velocity (AFr) were derived as $E/(E + A)$ and $A/(E + A)$, respectively.

Pulmonary venous waveforms were analyzed for the peak and integrated systolic (I) and diastolic (K) velocities, and their respective ratios (I/K) were derived. When necessary, integrals were calculated by dropping a vertical line to the baseline from the intersection of the systolic and diastolic waveforms. The fractional pulmonary venous velocity time integral during ventricular systole (FrJ) and diastole (FrK) was taken as the reservoir fraction, and the fractional pulmonary venous velocity time integral during diastole (FrK) was taken as the conduit fraction (12, 21).

Statistical Analysis

Hemodynamic, dimension, and echocardiographic data in atrial myopathic and sham-operated dogs were compared with unpaired t-tests. Calcium chloride data were compared with paired t-tests. All data are means ± SD. A P value < 0.05 was taken to indicate statistical significance.

**Table 2.** LA function variables at a matched LAP of 10 mmHg in myopathic and sham-operated dogs

<table>
<thead>
<tr>
<th></th>
<th>AMYO</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>$L_{A_{max}}$, ml</td>
<td>$9.7 ± 5.2$</td>
<td>$7.9 ± 4.4$</td>
</tr>
<tr>
<td>$L_{ASV}$, ml</td>
<td>$-0.21 ± 0.3^*$</td>
<td>$0.86 ± 0.50$</td>
</tr>
<tr>
<td>LAEF, %</td>
<td>$-3.0 ± 4.9^*$</td>
<td>$13.0 ± 4.0$</td>
</tr>
<tr>
<td>MNSER, $\text{vol/s}$</td>
<td>$-0.49 ± 0.66^*$</td>
<td>$2.8 ± 1.2$</td>
</tr>
<tr>
<td>$\text{Res}_{10}$, mmHg/ml</td>
<td>$0.05 ± 0.05^*$</td>
<td>$0.35 ± 0.06$</td>
</tr>
<tr>
<td>$k_c$, mmHg/ml</td>
<td>$0.97 ± 0.05^*$</td>
<td>$0.50 ± 0.14$</td>
</tr>
<tr>
<td>$k_c^*$, mmHg/ml</td>
<td>$5.7 ± 2.3^*$</td>
<td>$3.4 ± 0.6$</td>
</tr>
</tbody>
</table>

Data are means ± SD; *n = no. of dogs. AMYO, atrial myopathy; Sham, sham-operated dogs; $L_{A_{max}}$, maximal left atrial volume; $L_{ASV}$, LA stroke volume; LAEF, LA ejection fraction; MNSER, mean normalized systolic ejection rate; Res10, reservoir volume fraction at a LA pressure of 10 mmHg; $k$, atrial stiffness constants calculated with a pressure offset; $k_c$, normalized stiffness constant. *P < 0.05 vs. sham.
RESULTS

Hemodynamic, LV, and LA Functional Variables

Hemodynamic and LA functional data are presented in Tables 1 and 2 and representative examples of each are shown in Fig. 1. When compared with sham-operated controls at matched heart rates, rapidly paced (i.e., 400 beats/min for 6 wk) dogs had a slightly greater LAmax dimension and diastolic stiffness constant and significantly reduced reservoir volume; importantly, atrial systolic shortening was absent. In contrast, LV systolic pressure, peak positive dP/dt, the LV diastolic kc, and the time constant of LV isovolumic relaxation were similar. Thus, despite maintenance of LV systolic and diastolic function, LA systolic function was markedly impaired after 6 wk of rapid pacing.

LA pressure volume loops in rapidly paced dogs were characterized by a single clockwise V loop, with an area of 4.0±3.7 mmHg/ml (Fig. 2B). In contrast, a typical figure-eight shape, with a counterclockwise A loop and a clockwise V loop, was seen in sham control dogs (Fig. 2B); the A and V loop areas in these animals were 3.2±2.8 and 3.9±2.5 mmHg/ml, respectively. V loop areas were similar in rapidly paced dogs and sham control dogs.

The results for the four animals with AV nodal ablation and right atrial and ventricular pacemakers (Table 3) confirm those reported for dogs receiving calcium channel blockers.

Echocardiographic Data

Table 3. LA atrial hemodynamics in dogs with atrioventricular nodal blockade and atrioventricular sequential pacing

<table>
<thead>
<tr>
<th></th>
<th>HR, beats/min</th>
<th>LV dP/dt, mmHg/s</th>
<th>LAmax, ml</th>
<th>LASV, ml</th>
<th>LAEF, %</th>
<th>MNSER, vol/s</th>
<th>Res10, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMY0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>72</td>
<td>1,325</td>
<td>15.7</td>
<td>0.1</td>
<td>1.0</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>Dog 2</td>
<td>72</td>
<td>1,500</td>
<td>8.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog 3</td>
<td>72</td>
<td>1,875</td>
<td>9.5</td>
<td>1.5</td>
<td>17.8</td>
<td>6.87</td>
<td>0.35</td>
</tr>
<tr>
<td>Dog 4</td>
<td>72</td>
<td>1,250</td>
<td>15.2</td>
<td>1.4</td>
<td>9.9</td>
<td>4.09</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Table 4. Transmitral and LA appendage Doppler flow at a matched LAP about 10 mmHg in myopathic and sham-operated dogs

<table>
<thead>
<tr>
<th></th>
<th>AMY0 (n = 8)</th>
<th>Sham (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak E, cm/s</td>
<td>60.8±24.9</td>
<td>78.5±6.9</td>
</tr>
<tr>
<td>Peak A, cm/s</td>
<td>15.3±8.0</td>
<td>50.2±14.8*</td>
</tr>
<tr>
<td>Peak E/A</td>
<td>3.4±1.8</td>
<td>1.6±0.4*</td>
</tr>
<tr>
<td>Evti</td>
<td>4.1±1.2</td>
<td>5.3±2.0</td>
</tr>
<tr>
<td>Aventi</td>
<td>0.6±0.4</td>
<td>3.1±1.7*</td>
</tr>
<tr>
<td>E/Aventi</td>
<td>8.1±3.0</td>
<td>1.8±0.3*</td>
</tr>
<tr>
<td>Ex</td>
<td>0.88±0.04</td>
<td>0.64±0.03*</td>
</tr>
<tr>
<td>Ax</td>
<td>0.12±0.04</td>
<td>0.36±0.03*</td>
</tr>
<tr>
<td>E+Ax</td>
<td>4.3±0.8</td>
<td>8.4±3.9*</td>
</tr>
<tr>
<td>PVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>94±9</td>
<td>97±16</td>
</tr>
<tr>
<td>LAP, mmHg</td>
<td>12.0±1.8</td>
<td>11.0±1.4</td>
</tr>
<tr>
<td>Peak J, cm/s</td>
<td>24.0±6.1</td>
<td>41.3±4.0*</td>
</tr>
<tr>
<td>Peak K, cm/s</td>
<td>49.4±14.6</td>
<td>57.3±14.3</td>
</tr>
<tr>
<td>Peak J/K</td>
<td>0.50±0.13</td>
<td>0.75±0.22*</td>
</tr>
<tr>
<td>Jviti</td>
<td>3.3±1.1</td>
<td>6.1±1.3*</td>
</tr>
<tr>
<td>Kviti</td>
<td>9.1±3.5</td>
<td>9.4±2.3</td>
</tr>
<tr>
<td>Jx</td>
<td>0.41±0.19</td>
<td>0.66±0.23*</td>
</tr>
<tr>
<td>Ex</td>
<td>0.27±0.09</td>
<td>0.40±0.08*</td>
</tr>
<tr>
<td>Fx</td>
<td>0.73±0.09</td>
<td>0.60±0.07*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of dogs. MF, transmitral flow; PVF, pulmonary venous flow; E, early diastolic velocity; A, late diastolic velocity; vti, velocity time integral; Fx, fractional filling; J, systolic velocity; K, diastolic velocity; Res, reservoir function; Cond, conduit function. Other abbreviation as in Table 1. *P < 0.05 vs. sham.
DISCUSSION

The principal finding of this study is that 6 wk of rapid (400 beats/min) atrial pacing and a normal ventricular rate response produce an isolated atrial cardiomyopathy characterized by impaired booster pump and reservoir functions and increased chamber stiffness and relative conduit function. The model mimics the effects of rapid atrial tachycardias, such as atrial flutter and fibrillation independently of ventricular function; this is important insofar as in our previous study (14), ventricular dysfunction produced compensatory increases in LA function. Further studies are needed to determine whether the atrial myopathy observed in this study may be modulated by the adaptive (and directionally opposite) LA functional changes that occur in response to coexisting LV dysfunction.

The loss of atrial booster pump function at the paced heart rates as assessed by sonomicrometry precluded measurement of atrial “A” wave pressure-volume loop areas and atrial systolic elastance; indeed, atrial ejection phase indexes indicated that the LA body failed to shorten during atrial systole. Thus net atrial work (A-V loop area) was negative in atrial myopathic dogs; these data indicate that net work was performed on the left atrium and suggest that atrial efficiency is considerably reduced in this model (24). The altered Doppler filling indexes confirm the severe impairment of atrial contractile function in these animals. However, further work is needed to determine the effect of atrial inefficiency on LV systolic performance.

The present study also indicates that decreased diastolic LA compliance (increased stiffness constant), impaired atrial reservoir function (decreased reservoir fraction), and relative increases in the conduit-to-reservoir capacity as assessed from the pulmonary vein Doppler occur in the absence of LA hypertrophy. To compare chamber stiffnesses of left atria with different unstressed volumes, we performed a volume normalization and compared stiffness over a common level of LA pressure. Thus the observed differences did not result from differences in operative compliance. The contribu-

Table 5. Calcium effects on hemodynamic and LV and LA functional variables in atrial myopathic dogs

<table>
<thead>
<tr>
<th></th>
<th>HR, beats/min</th>
<th>LAP, mmHg</th>
<th>LVSP, mmHg</th>
<th>LV dP/dt, mmHg/s</th>
<th>LVSF, %</th>
<th>t, ms</th>
<th>LAMAX, ml</th>
<th>LASV, ml</th>
<th>LAEF, %</th>
<th>MNSER, vol/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>97 ± 16</td>
<td>10.6 ± 4.9</td>
<td>100 ± 7*</td>
<td>1.320 ± 256*</td>
<td>6.0 ± 2.0*</td>
<td>42.8 ± 3.5</td>
<td>8.1 ± 1.7</td>
<td>0.09 ± 0.07*</td>
<td>1.2 ± 0.9*</td>
<td>0.30 ± 0.37*</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>94 ± 21</td>
<td>14.6 ± 5.1</td>
<td>127 ± 22</td>
<td>1.860 ± 233</td>
<td>7.7 ± 2.7</td>
<td>41.1 ± 4.7</td>
<td>8.8 ± 2.0</td>
<td>0.39 ± 0.15</td>
<td>4.7 ± 1.8</td>
<td>0.85 ± 0.19</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, 5 dogs. *P < 0.05 vs. Ca²⁺.

Table 6. Calcium effects on hemodynamic and LV and LA functional variables in historical control dog

<table>
<thead>
<tr>
<th></th>
<th>LVSP, mmHg</th>
<th>LV dP/dt, mmHg/s</th>
<th>HR, beats/min</th>
<th>LASV, ml</th>
<th>LAEF, %</th>
<th>MNSER, vol/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>115 ± 14</td>
<td>1,214 ± 122</td>
<td>106 ± 9</td>
<td>0.8 ± 0.2</td>
<td>11.3 ± 2.7</td>
<td>2.1 ± 0.6</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>134 ± 21*</td>
<td>1,800 ± 363*</td>
<td>103 ± 5</td>
<td>1.3 ± 0.3*</td>
<td>19.0 ± 4.1*</td>
<td>2.8 ± 0.8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, 7 dogs. See Refs. 11 and 14 for additional information. *P < 0.05 vs. baseline.
tions of abnormalities intrinsic and extrinsic to atrial myocardium that are responsible for the reduced distensibility of the left atrium await further study.

We previously showed that calcium infusion causes significant increases in atrial systolic elastance, stroke volume, ejection fraction, and mean ejection rate (14). However, in the present study, atrial shortening indexes during maximal calcium infusion were markedly attenuated. These data are consistent with those from a previous study in which impaired responsiveness to calcium was demonstrated in ventricular trabeculae from dogs with pacing-induced ventricular failure (22). The positive inotropic effectiveness of calcium in our study is evident insofar as indexes of ventricular systolic function were increased and indicates that rapid pacing produces impaired atrial but not ventricular inotropic function to noncatecholamine-mediated stimulation.

Our study provides the first detailed characterization of the functional correlates that accompany the electrophysiological and ultrastructural changes in this model. Although similar models have been described in both the goat and dog, atrial mechanical function in these models has not been directly characterized (19, 27). Decreased atrial refractoriness, increased intra-atrial conduction time, increased susceptibility to and maintenance of atrial fibrillation, and evidence of sinus node dysfunction are associated with a variety of atrial ultrastructural abnormalities, including myocyte hypertrophy, fibrosis, and myofiber disarray (4, 19, 27, 28). Although a marked increase in atrial size was previously demonstrated echocardiographically (19), the abnormalities of atrial systolic reservoir and conduit functions that we report have implications for atrial arrhythmia risk factor assessment and management and for understanding the genesis of atrial arrhythmias.

The mechanism responsible for the atrial abnormalities is not completely understood. Atrial stunning and impaired calcium homeostasis have been implicated, but other mechanisms such as neurohormonal and ultrastructural changes resulting from increased atrial pressure and stretch, and the rapid pacing rates, per se, may be responsible (20). In this regard, it is interesting that the functional changes at 6 wk were similar in many respects to those changes occurring after 1 wk of pacing (9). Of interest, a linear relationship between pacing duration and the duration of induced atrial fibrillation was recently reported (4). Therefore, it is likely that the duration of pacing-induced tachycardia produces a spectrum of disease and that the early changes facilitate the mechanical and electrophysiological alterations that eventuate in structural changes in the atrium. This hypothesis warrants additional testing.

Limitations

There are several potential limitations of this study. First, we used calcium channel blockers to slow the ventricular response. Although these agents depress myocardial contractility, a recent study suggests that impaired atrial contractility after short-term atrial fibrillation is attenuated by calcium channel blockade. Therefore, it is important that both sham-operated control dogs and experimental animals were given diltiazem; verapamil was avoided in these animals because of the frequency-dependent myocardial depression associated with its use (1). Moreover, the findings in the dogs studied with AV nodal blockade and atrial and ventricular pacemakers support the conclusions of the larger study. Second, improper alignment of LV epicardial and LA diameter gauges produce inaccurate estimates of absolute LV and LA volume, respectively. However, the analytic methods we employed are not dependent on absolute volume determinations. Third, because of the complex instrumentation required, terminal hemodynamic studies were performed in anesthetized, open chest animals. Despite the cardiodepression and blunted reflexes associated with anesthesia (25), time-dependent hemodynamic changes are qualitatively similar in conscious and anesthetized animals. A related potential problem relates to the loss of pericardial influences on reservoir and conduit functions in the terminal studies. Although we recently demonstrated that the pericardium reduces atrial compliance and that pericardial restraint increases directly with atrial volume (13), the present study was performed with a widely opened pericardium; thus, pericardial effects cannot account for our findings. Nevertheless, it is important that data are extrapolated cautiously from these animal models in human disease. Finally, the use of a simple exponential to describe diastolic pressure and volume behavior is potentially limited because it has little physiological basis (5). However, we were primarily interested in demonstrating that for a similar range of LV diastolic pressures and volumes, there was no difference in a frequently used parameter of chamber stiffness.

In conclusion, despite these limitations, we have shown that rapid pacing produces an atrial myopathy characterized by impaired atrial systolic function, diastolic stiffness, and altered atrial reservoir to conduit functions in the context of normal ventricular function. Simultaneous rapid atrial and ventricular pacing should be feasible with experimentally produced AV block and will allow the investigation of a range of atrial and ventricular functions that accompany human atrial arrhythmias.

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