Experimental congestive heart failure produced by rapid ventricular pacing in the dog: cardiac effects

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ABSTRACT Chronic rapid ventricular pacing in the dog reportedly produces a useful preparation of low-output heart failure. However, little information is available regarding cardiac changes in this preparation. Accordingly, we evaluated the effects of both short-term (3 weeks) and prolonged (2 months) rapid ventricular pacing on cardiac hemodynamics, mass, and chamber size. The effects of short-term pacing on left ventricular wall thickening, blood flow, and metabolism were also examined. Compared with 16 control dogs, dogs paced for either 3 weeks (n = 8) or 2 months (n = 13) exhibited reduced cardiac outputs (control 130 ± 20 ml/min/kg, 3 week pacing 112 ± 19 ml/min/kg, 2 month pacing 116 ± 14 ml/min/kg) and elevated pulmonary wedge pressures (control 10 ± 3 mm Hg, 3 week pacing 26 ± 5 mm Hg, 2 month pacing 26 ± 8 mm Hg) and right atrial pressures (control 4 ± 1 mm Hg, 3 week pacing 13 ± 3 mm Hg, 2 month pacing 9 ± 3 mm Hg) (all p < .01 vs control). At the postmortem examination, both groups of paced dogs also exhibited increased left ventricular volumes (control 13 ± 6 ml, 3 week pacing 27 ± 6 ml, 2 month pacing 26 ± 8 ml), right ventricular volumes (control 13 ± 5 ml, 3 week pacing 27 ± 9, 2 month pacing 24 ± 7 ml), and right ventricular mass (control 27 ± 5 g, 3 week pacing 32 ± 6 g, 2 month pacing 34 ± 6 g) (all p < .03 vs control) but had normal left ventricular mass. Three weeks of pacing also decreased percent left ventricular shortening (34 ± 6% to 17 ± 7%) associated with a disproportionate deterioration of posterior wall thickening (58 ± 16% to 17 ± 18%) (both p < .01), as assessed by echocardiography. This left ventricular dysfunction was associated with no change in myocardial lactate extraction (preparing 40 ± 10%, 3 week pacing 36 ± 10%), myocardial arteriovenous O₂ difference, or myocardial histology, suggesting that it was not due to myocardial ischemia. These data indicate that rapid ventricular pacing in the dog produces a useful experimental preparation of low-output heart failure characterized by biventricular pump dysfunction, biventricular cardiac dilation, and nonischemic impairment of left ventricular contractility.

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A VARIETY of canine experimental preparations of congestive heart failure have been developed. However, most of these preparations have major limitations. Those based on volume and pressure overloading are technically complicated since it is difficult to control the degree of overloading, and those based on production of venous obstruction and/or right heart failure may not resemble heart failure in man, which usually affects the left ventricle. Preparations based on myocardial damage with toxins or ischemia are limited since such insults frequently produce either too little damage or high early mortality due to damage that is too extensive.

Several recent studies suggest that chronic rapid ventricular pacing in the dog may produce a technically simpler, more predictable, and more stable preparation of heart failure than has previously been available. Specifically, Rieger and his colleagues demonstrated that ventricular pacing at 240 to 280 beats/min for 2 weeks in six dogs produced hemodynamic and neurohumoral changes similar to those observed with biventricular cardiac dysfunction in man. An additional attractive feature of this preparation was that pump dysfunction and fluid retention appeared to be reversed by discontinuing pacing.
However, little information is available about cardiac changes in this preparation. Therefore, in the present study we sought to characterize the effect of both short-term (3 weeks) and prolonged (2 months) rapid ventricular pacing on cardiac size, mass, function, and metabolism in the dog.

Methods

Forty-six adult male mongrel dogs (weight 18 to 25 kg) were studied. Sixteen were used as control animals. Seventeen dogs were used to study the effects of 3 weeks of rapid ventricular pacing. Thirteen were used to study the effect of pacing for 2 months. Twenty-eight of the dogs were also trained to walk on a treadmill and had electromagnetic femoral artery flow probes inserted for exercise studies. Results of the exercise studies are reported elsewhere.7

Three week pacing protocols. A total of 17 dogs was studied. Before instrumentation, baseline cardiac M mode echocardiograms were performed with the dogs awake and sitting upright on their hind legs. Left ventricular echocardiograms were obtained at the chordal level just below the tips of the mitral leaflet. In six of the dogs, both two-dimensional guided M mode and two-dimensional short-axis echocardiograms were obtained with a Hanninson mechanical echocardiograph.

Immediately after the echocardiographic examination, dogs were anesthetized with pentobarbital (30 mg/kg). A ventricular pacing lead (Medtronic sutureless type) was attached to the left ventricular apex through a 3 to 4 cm long left thoracotomy; the lead was tunneled to the back and connected to a subcutaneously implanted Medtronic multiprogrammable pulse generator. After recovery from anesthesia, the dogs were returned to a chronic care facility where they received a standard diet and free access to water.

In eight dogs, the pacemaker was programmed to pace at 260 beats/min within 24 hr of pacemaker insertion. Three weeks later, the pacemaker was reprogrammed to 30 beats/min and a repeat echocardiographic examination was performed. The dogs were then lightly anesthetized with pentobarbital (10 mg/kg). Under fluoroscopy, a thermodilution Swan-Ganz catheter (Edwards) was inserted via the left external jugular vein and positioned in the pulmonary artery. A polyethylene catheter was inserted via the right carotid artery and positioned in the descending aorta. Catheters were secured to the skin, anesthesia was terminated, and the pacemaker was reprogrammed to 260 beats/min.

Two days later, hemodynamic studies were performed with the dogs standing quietly. Arterial pressure, right atrial pressure (proximal Swan-Ganz port), pulmonary arterial and wedge pressures, and cardiac outputs were measured. Cardiac outputs were measured in triplicate with the use of 5 ml injectates of iced dextrose and an Edwards thermodilution computer. Thermodilution decay curves were displayed to ensure accurate mixing. Results of the three outputs were averaged. At the end of the study, dogs were killed by the administration of 100 ml of 5% sodium chloride, an intervention that arrests the heart in dia-stole. The heart was then excised and analyzed as described below.

Studies in these initial eight dogs indicated that pacing produced distinctive echocardiographic and hemodynamic abnormalities. To determine the time course of these abnormalities and their reversibility after termination of pacing, three dogs were returned to the laboratory 2 to 3 days after insertion of the pacemaker. Under light pentobarbital anesthesia (10 mg/kg), a Swan-Ganz catheter was inserted through a jugular vein of each, and a short polyethylene catheter was inserted into a femoral artery. Intracardiac and arterial pressures and thermodilution cardiac outputs were measured. Anesthesia was terminated, the pacemaker was programmed to pace at 260 beats/min, and the dogs were returned to the chronic care facility.

At 1 and 2 weeks after initiation of pacing, echocardiographic examinations were performed in dogs fully awake and with the pacemakers temporarily reprogrammed to 30 beats/min for the study. At 3 weeks, another echocardiographic study was performed, after which the dogs were lightly anesthetized with pentobarbital and hemodynamic measurements were made while the dog’s heart was being paced at 260 beats/min. The pacemaker was then reprogrammed to pace at 30 beats/min and anesthesia was terminated. Repeat M mode echo studies were performed at 3, 5, 7, 14, and 21 days after termination of pacing. Central hemodynamic measurements were also obtained under light pentobarbital anesthesia at 1 and 2 weeks after pacing.

After demonstration that pacing produced left ventricular dysfunction, six dogs were studied to investigate the mechanism responsible for this dysfunction. One week after initial pacemaker implantation, dogs were lightly anesthetized with pentobarbital (3 to 5 mg/kg) and morphine sulfate (6 mg/kg). A Wilton-Webster coronary sinus thermocatheter was inserted via a jugular vein and guided under fluoroscopy into the proximal coronary sinus. A Swan-Ganz catheter was inserted via a femoral vein and advanced to the pulmonary artery. A short polyethylene catheter was inserted into a femoral artery.

After instrumentation, baseline measurements of coronary sinus blood flow, arterial blood pressure, pulmonary arterial and wedge pressures, right atrial pressures, and cardiac outputs were obtained. Arterial, coronary sinus, and pulmonary arterial blood samples were obtained for measurement of hemoglobin oxygen saturation and lactate. Control measurements were repeated every 10 min for a total of 30 min. The pacemaker was then programmed to pace at 260 beats/min, and all measurements were repeated at 10, 20, and 30 min of pacing. The pacing rate was reduced to 30 beats/min. Anesthesia was terminated, and the dog was returned to a chronic care facility.

Twenty-four hours later, the pacemaker was programmed to pace at 260 beats/min. After 3 weeks of pacing, M mode echocardiographic studies were repeated while the pacemaker was temporarily reprogrammed to pace at 30 beats/min. The following day, the dogs were again anesthetized with pentobarbital (3 to 5 mg/kg) and morphine sulfate (6 mg/kg) and instrumented as described previously. Three sets of hemodynamic and coronary measurements were obtained 10 min apart at a pacing rate of 260 beats/min. Pacing was then terminated, and measurements were made at 10, 20, and 30 min after termination of pacing. Repeated measurements made at each observation period during both the initial and terminal studies were stable and therefore were averaged.

Two month pacing protocol. Thirteen dogs were studied. Pacemakers were inserted as described above. Twenty-four hours after pacemaker insertion, dogs were programmed to pace at 240 beats/min. Over the following 2 months, they were monitored closely for the development of severe ascites, respiratory distress, or anorexia. During pilot studies, it was noted that dogs who developed these changes frequently died from pulmonary edema. Accordingly, pacing rates were adjusted downward to a minimum rate of 220 beats/min in the event that marked ascites, anorexia, and/or respiratory distress developed.

At 2 months, dogs were temporarily reprogrammed to a pacing rate of 30 and then were lightly anesthetized with morphine sulfate (4 mg/kg). Swan-Ganz and arterial catheters were inserted and anesthesia was reversed with use of 1 to 2 mg naloxone hydrochloride. The dogs were reprogrammed to their previous pacing rate and resting, upright, awake hemodynamic measure-
ments were made 24 to 48 hr later, as described previously. Each dog was then killed with cadmium chloride and the heart was excised.

Control protocol. Sixteen dogs served as controls. After pacemaker implantation, dogs were kept in the chronic care facility for 2 to 3 weeks. At the end of this time, they were lightly anesthetized with pentobarbital (10 mg/kg). Swan-Ganz and arterial catheters were inserted and anesthesia was terminated. Resting, upright, awake hemodynamic measurements were made 24 to 48 hr later. Each was then killed with cadmium chloride and the heart was excised for postmortem evaluation.

In eight of the dogs, M mode echocardiograms were also obtained before and 3 weeks after pacemaker insertion. Two-dimensional studies were obtained at these same two times in four of the eight dogs.

Gross and microscopic cardiac examination. After excision of the heart, the great vessels were removed at the level of the aortic and pulmonary arterial valves. The heart was weighed and then fixed in a 3.75% formaldehyde solution for 2 weeks. The coronary arteries were sectioned at 0.5 cm intervals to exclude thrombus formation. The entire heart was then sectioned perpendicular to the long axis with a slicing machine and processed by a modification of the technique described by Janicki et al. Each section was 4 to 5 mm in thickness. The thickness of each section was measured at four sites with a Vernier caliper and averaged. Slices from each heart were then placed on a clear plastic sheet, along with a scale marker, and sectioned. The endocardial outlines of the right and left ventricles were digitized with a Hewlett-Packard digitizer, and the area within each chamber was calculated. This chamber area was multiplied by the section thickness to obtain the chamber volume.

Left and right ventricular volumes for each section were then summed to obtain the total chamber volume. The right ventricular free wall was dissected from the septum on each section and both the free wall and the remaining left ventricle were weighed. These section weights were summed to obtain total left ventricular and septal and total right ventricular free wall weights.

In three of the control dogs and in the three paced dogs with the most severe posterior basal left ventricular dysfunction, 2 cm long sections from the posterior basal left ventricle just above the papillary muscle were processed for histologic examination and were then examined by light microscopy for evidence of myocardial infarction (wavy fibers, contraction bands, neutrophilic infiltrates, or interstitial fibrosis).

M Mode echocardiographic measurements. All M mode echocardiograms were analyzed by one of us (P. D.). The investigator was blinded to the temporal sequence of echocardiograms in each dog but was permitted to compare all echocardiographs from each dog to ensure that tracings were marked at the same level within the left ventricle. Left ventricular dimension was marked at the chordal level just below the tips of the mitral valve. The right and left septum, posterior wall endocardium, and posterior wall epicardium were marked at end-systole and end-diastole for 4 to 5 consecutive cardiac cycles. End-systole was identified as the smallest cavity dimension while end-diastole was taken as the cavity dimension just before the onset of posterior wall and septal thickening. Tracings were then digitized with a Hewlett-Packard digitizer, results were averaged, and left ventricular end-diastolic (DD) and end-systolic (DS) dimension, percent left ventricular shortening ([DD - DS] × 100/DD), posterior wall thickness, septal thickness, percent posterior wall shortening, and percent septal shortening were calculated.

Quantitative analysis of two-dimensional echocardiograms. Short-axis two-dimensional echocardiograms were analyzed by an approach similar to that previously described by Nieminen and Haendchen and their colleagues. In all analyses, end-diastole was defined as the largest cavity image and end-systole was defined as the smallest. Epicardial and endocardial outlines of the two-dimensional echocardiogram at the mid-papillary level were manually traced from stop-frame images on the screen onto clear plastic sheets. The outlines were then digitized into a Hewlett-Packard computer system for analyses. For each echocardiographic examination, five end-diastolic and five end-systolic outlines were digitized.

Once the outlines were digitized, the insertion of the anterior papillary muscle was identified. The point on the lateral left ventricular wall was identified that, when connected to the anterolateral insertion point of the papillary muscle, divided the left ventricular cavity into two equal areas. These two points were joined by a line. The midpoint of this bisecting line was identified and additional bisecting lines were constructed every 30° so that the left ventricular wall was divided into 12 segments (figure 1). The mean wall thickness in each segment was then calculated for each of the five diastolic and systolic outlines obtained from each study. All diastolic and all systolic thicknesses were averaged. Percent thickening of each segment was then calculated as (mean end-systolic thickness − mean end-diastolic thickness) × 100.

Measured variables. Hemoglobin concentration and O₂ saturation were measured with an Instrumentation Laboratory 282 Co-oximeter programmed for canine blood. The instrument was calibrated before each experiment with analytic reference samples. Blood lactate was analyzed by a spectrophotometric technique. Arteriovenous oxygen difference was calculated as Hb × 1.34 ml O₂ (arterial-venous O₂ saturation). Systemic oxygen consumption (VO₂) was calculated as cardiac output × arteriovenous O₂ difference. Systemic vascular resistance was calculated as (mean arterial-right atrial pressure) / cardiac output. Coronary sinus blood flow was determined by a thermodilution technique with use of a continuous infusion of room temperature 5% dextrose in water at a rate of 38 ml/min. Flow was calculated with the equation of Ganz et al. Myocardial VO₂ was calculated as coronary sinus blood flow × arteriovenous O₂ difference. Percentage myocardial lactate extraction

**FIGURE 1.** Segment distribution used in the two-dimensional echocardiographic analysis.
was calculated as $100 \times (\text{arterial} - \text{coronary sinus lactate})/\text{arterial lactate}.$

**Statistical analysis.** Values are presented as the mean ± SD. Differences between single measurements in control dogs and those with heart failure were compared by nonpaired Student's t testing. Changes within the same dogs were analyzed by paired Student's t testing. Myocardial flow and metabolic data were analyzed by repeated-measures analysis of variance; subsequent paired comparisons were made by the Bonferroni method. A probability value of $< .05$ was considered indicative of a significant difference.

**Results**

Over 2 to 3 weeks of observation, there was no change in weight in the 16 control dogs ($20.1 \pm 2.0$ to $20.0 \pm 2.0$ kg, $p = \text{NS}$). There was also no change in the 17 dogs who were paced for 3 weeks ($19.8 \pm 2.1$ to $21.1 \pm 3.8$ kg, $p = \text{NS}$). However, ascites developed in 15 of the dogs ($2.2 \pm 2.5$ liters). In the 13 dogs who were paced for 2 months there was an increase in weight from $19.0 \pm 2.0$ to $21.6 \pm 4.2$ kg ($p < .05$), with ascites developing in 11 of the 13 dogs ($3.4 \pm 3.0$ liter).

**Hemodynamic effects of pacing.** Resting awake hemodynamic measurements were obtained in 16 control dogs, eight dogs paced for 3 weeks, and 13 dogs paced for 2 months (table 1). In the control dogs, mean arterial pressure averaged $115 \pm 21$ mm Hg, pulmonary wedge pressure $10 \pm 3$ mm Hg, right atrial pressure $4 \pm 1$ mm Hg, and cardiac output $130 \pm 20$ ml/min/kg. In contrast, the dogs who were paced for 3 weeks exhibited reduced mean arterial pressures ($93 \pm 10$ mm Hg) and cardiac outputs ($112 \pm 19$ ml/min/kg) and elevated pulmonary arterial wedge ($26 \pm 5$ mm Hg), and right atrial ($13 \pm 3$ mm Hg) pressures (all $p < .01$ vs control).

**TABLE 1**  
Resting awake hemodynamic measurements obtained in control dogs, dogs paced for 3 weeks, and dogs paced for 2 months

<table>
<thead>
<tr>
<th></th>
<th>Control dogs (n = 16)</th>
<th>Pacing for 3 weeks (n = 8)$^a$</th>
<th>Pacing for 2 months (n = 13)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>125 ± 15</td>
<td>263 ± 6$^c$</td>
<td>222 ± 12$^c$</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>115 ± 21</td>
<td>93 ± 10$^c$</td>
<td>101 ± 13</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>4 ± 1</td>
<td>13 ± 3$^c$</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>10 ± 3</td>
<td>26 ± 5$^b$</td>
<td>26 ± 8$^b$</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg)</td>
<td>130 ± 20</td>
<td>112 ± 19$^c$</td>
<td>116 ± 14$^c$</td>
</tr>
<tr>
<td>Arteriovenous $\text{O}_2$ difference (ml/dl)</td>
<td>6.0 ± 1.4</td>
<td>8.6 ± 1.2$^c$</td>
<td>7.7 ± 1.9$^b$</td>
</tr>
<tr>
<td>Systemic $\text{O}_2$ (ml/min/kg)</td>
<td>8 ± 2</td>
<td>10 ± 2</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Systemic vascular resistance (units)</td>
<td>37 ± 8</td>
<td>37 ± 9</td>
<td>40 ± 7</td>
</tr>
</tbody>
</table>

$^a$Measurements were made with pacemakers activated.

$^b$Measurements were made with pacemakers activated.

$^c$p < .05 vs control; $^d$p < .01 vs control.

**TABLE 2**  
Effect of acute versus 3 weeks of rapid ventricular pacing on systemic hemodynamics in dogs anesthetized with morphine sulfate

<table>
<thead>
<tr>
<th></th>
<th>Control dogs (n = 6)</th>
<th>Acute pacing (n = 6)</th>
<th>3 weeks of pacing (n = 5)</th>
<th>Pacemaker off (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 11</td>
<td>260 ± 0$^b$</td>
<td>260 ± 0$^b$</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>85 ± 7</td>
<td>74 ± 6$^b$</td>
<td>82 ± 12$^b$</td>
<td>85 ± 14</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>9 ± 3</td>
<td>20 ± 3$^b$</td>
<td>25 ± 7$^b$</td>
<td>20 ± 5$^b$</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>8 ± 2</td>
<td>11 ± 3$^b$</td>
<td>18 ± 3$^b$</td>
<td>16 ± 1$^b$</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg)</td>
<td>93 ± 16</td>
<td>68 ± 6$^b$</td>
<td>67 ± 19$^a$</td>
<td>70 ± 17$^a$</td>
</tr>
<tr>
<td>Systemic $\text{O}_2$ (ml/min/kg)</td>
<td>4.7 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>6.7 ± 0.5</td>
<td>5.7 ± 0.9</td>
</tr>
</tbody>
</table>

$^a$p < .05 vs control; $^b$p < .01 vs control.

< .01 vs control). Hemodynamic changes were similar in paced dogs for 2 months except that the arterial blood pressure was not significantly reduced in these dogs.

The immediate versus long-term effect on hemodynamic measurements of pacing dogs at 260 beats/min was examined in six dogs (table 2). All measurements were made in dogs under light morphine sulfate anesthesia.

Acute onset of pacing at a rate of 260 beats/min resulted in an immediate decrease in arterial blood pressure and cardiac output and increases in right atrial and pulmonary wedge pressure. After 3 weeks of pacing, dogs exhibited reductions in cardiac output similar to those noted with acute pacing. However, pulmonary wedge, right atrial, and mean arterial blood pressure were all higher than with acute pacing. When pacing was terminated, all measurements remained unchanged over the subsequent 30 min period of observation.

Serial hemodynamic measurements were made in three dogs under light anesthesia to examine the effect of terminating pacing for a prolonged period. As illustrated in figure 2, 3 weeks of pacing increased intracardiac pressures and decreased the cardiac output. When pacing was terminated, all pressure measurements returned to control levels within 1 to 2 weeks. In contrast, cardiac outputs tended to be higher than during the control study.
M mode echocardiographic changes (table 4). Technically adequate M mode echocardiographic studies were obtained in eight control dogs and 15 dogs paced for 3 weeks. In the control dogs, baseline left ventricular diastolic dimension averaged \(3.2 \pm 0.4\) cm and left ventricular percent shortening 37 \(\pm 3\%\). No significant change in any echocardiographic measurement was noted at 3 weeks.

The paced dogs had baseline left ventricular echocardiographic measurements comparable to those observed in the control dogs. Pacing produced an increase in left ventricular diastolic dimension from 3.6 \(\pm 0.4\) to 4.3 \(\pm 0.6\) cm (\(p < .001\)) and a decrease in left ventricular shortening from 33 \(\pm 5\%\) to 18 \(\pm 6\%\) (\(p < .001\)). This decreased shortening was primarily due to a marked decrease in percent posterior wall thickening from 56 \(\pm 14\%\) to 15 \(\pm 16\%\) (\(p < .001\)). No change in septal wall thickening was observed. Posterior and septal wall thickness also both decreased significantly with pacing.

Three dogs were studied serially to determine the time course of echocardiographic changes. As shown in figure 1, posterior wall thickening was impaired by 1 to 2 weeks of pacing, whereas left ventricular dilation occurred by 2 to 3 weeks. Termination of pacing resulted in a return of posterior wall function to normal levels by 1 to 2 weeks. Left ventricular diastolic dimension remained increased at the end of 3 weeks. Representative echocardiograms exhibiting serial changes in the M mode echograms are shown in figure 3.

Two-dimensional echocardiographic changes. Short-

Cardiac weight and chamber size (table 3). Measurements of postmortem cardiac weight and size were made in 16 control dogs, eight dogs paced for 3 weeks, and 13 dogs paced for 2 months. Before cardiac fixation, total cardiac weight was similar in all three groups. After fixation, there was also no difference between the three groups with respect to total cardiac weight and left ventricular weight. However, right ventricular free wall weight was significantly greater in dogs paced for 3 weeks and those paced for 2 months than in the control dogs; the increase in eight averaged approximately 20\% for both groups. Both pacing groups also exhibited over twofold greater left and right ventricular volumes than did the control dogs. In all dogs, epicardial coronary arteries were sectioned and were grossly normal.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Control dogs (n = 16)</th>
<th>3 weeks of pacing (n = 8)</th>
<th>2 months of pacing (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (g)</td>
<td>115 (\pm 21)</td>
<td>115 (\pm 16)</td>
<td>121 (\pm 13)</td>
</tr>
<tr>
<td>Total/BW (g/kg)</td>
<td>5.6 (\pm 1.1)</td>
<td>6.0 (\pm 0.7)</td>
<td>5.8 (\pm 1.3)</td>
</tr>
<tr>
<td>LV (g)</td>
<td>90 (\pm 17)</td>
<td>83 (\pm 12)</td>
<td>89 (\pm 10)</td>
</tr>
<tr>
<td>LV/BW (g/kg)</td>
<td>4.4 (\pm 0.8)</td>
<td>4.2 (\pm 0.6)</td>
<td>4.2 (\pm 1.0)</td>
</tr>
<tr>
<td>RV (g)</td>
<td>27 (\pm 5)</td>
<td>32 (\pm 6)(^a)</td>
<td>34 (\pm 6)(^b)</td>
</tr>
<tr>
<td>RV/BW (g/kg)</td>
<td>1.3 (\pm 0.2)</td>
<td>1.6 (\pm 0.3)(^a)</td>
<td>1.6 (\pm 0.3)(^a)</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV (ml)</td>
<td>12.9 (\pm 6.3)</td>
<td>27.3 (\pm 6.3)(^b)</td>
<td>25.5 (\pm 7.8)(^b)</td>
</tr>
<tr>
<td>LV/BW (ml/kg)</td>
<td>0.6 (\pm 0.3)</td>
<td>1.4 (\pm 0.3)(^b)</td>
<td>1.4 (\pm 0.3)(^b)</td>
</tr>
<tr>
<td>RV (ml)</td>
<td>12.6 (\pm 5.3)</td>
<td>26.6 (\pm 8.5)(^b)</td>
<td>23.9 (\pm 7.1)(^b)</td>
</tr>
<tr>
<td>RV/BW (ml/kg)</td>
<td>0.7 (\pm 0.3)</td>
<td>1.3 (\pm 0.4)(^b)</td>
<td>1.3 (\pm 0.4)(^b)</td>
</tr>
</tbody>
</table>

**BW** = body weight; **LV** = left ventricle; **RV** = right ventricle.

\(^a\)p < .03 vs control; \(^b\)p < .01 vs control.
axis two-dimensional echocardiograms at the level of the papillary muscles were obtained in four of the control dogs and six of the dogs that were paced for 3 weeks. At the time of baseline studies, left ventricular diastolic wall thickness and wall thickening were comparable in both groups. Wall thickening was noted to be most prominent in the posterior left ventricle (segments 3 to 7) (figure 4), as has been previously described. 10

At 3 weeks, there was no significant change in the control dogs either in wall thickness or in the degree of wall thickening. In contrast, in the paced dogs there was a marked reduction in percent wall thickening in all segments except Nos. 10 and 11. In addition, significantly reduced wall thickness was noted in six of 12 segments (figure 4).

An example of a two-dimensional echocardiographic study done before pacing and one obtained immediately after 3 weeks of pacing is shown in figure 5.

<table>
<thead>
<tr>
<th>TABLE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic changes in control dogs (n = 8) and dogs paced for 3 weeks (n = 16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control dogs</th>
<th></th>
<th>Paced dogs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>3 weeks</td>
<td>Base</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 20</td>
<td>115 ± 12</td>
<td>129 ± 22</td>
<td>166 ± 39*</td>
</tr>
<tr>
<td>LV diastolic dimension (cm)</td>
<td>3.22 ± 0.39</td>
<td>3.44 ± 0.48</td>
<td>3.60 ± 0.41</td>
<td>4.28 ± 0.56b</td>
</tr>
<tr>
<td>% LV shortening</td>
<td>37 ± 3</td>
<td>32 ± 4</td>
<td>33 ± 5</td>
<td>18 ± 6b</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.76 ± 0.19</td>
<td>0.72 ± 0.15</td>
<td>0.75 ± 0.13</td>
<td>0.67 ± 0.10a</td>
</tr>
<tr>
<td>% posterior wall thickening</td>
<td>59 ± 9</td>
<td>55 ± 19</td>
<td>56 ± 14</td>
<td>15 ± 16b</td>
</tr>
<tr>
<td>Septal wall thickness (cm)</td>
<td>0.81 ± 0.13</td>
<td>0.73 ± 0.10</td>
<td>0.83 ± 0.13</td>
<td>0.71 ± 0.12a</td>
</tr>
<tr>
<td>% septal thickening</td>
<td>43 ± 10</td>
<td>48 ± 33</td>
<td>40 ± 12</td>
<td>41 ± 17</td>
</tr>
</tbody>
</table>

Echocardiographic studies were performed with all dogs in sinus rhythm.

*p < .02 vs basal study; *p < .001 vs basal study.

Effect of pacing on left ventricular blood flow and metabolism. The acute effects of rapid ventricular pacing (260 beats/min) on left ventricular blood flow and metabolism were studied in six dogs under light morphine anesthesia. Pacing produced an immediate increase in coronary sinus blood flow and myocardial VO₂, but no change in myocardial arteriovenous oxygen difference or lactate extraction (table 5). Hemodynamic changes have already been summarized (table 2).

Pacing for 3 weeks at 260 beats/min produced ascites in all dogs and death due to pulmonary edema in one of the dogs. In the remaining five dogs, coronary blood flow and metabolism (table 5) and systemic hemodynamics (table 2) were reassessed at 3 weeks, again in dogs under light morphine anesthesia. At this time, myocardial VO₂ and flow were higher than with acute pacing, while the myocardial arteriovenous O₂ difference and lactate extraction were unchanged. Terminating pacing returned coronary sinus blood flow.
and myocardial VO₂ toward control levels, but again with no change in the myocardial arteriovenous O₂ difference or lactate extraction.

**Histology.** Light microscopic histologic examinations were performed on tissue samples taken from the posterior segment of the left ventricle in three control dogs and in the three paced dogs who exhibited the most marked impairment of posterior wall thickening on the echocardiogram. All sections examined revealed normal myocardium with no evidence of infarction, myofiber hypertropy, or fibrosis.

**Discussion**

In 1971, Coleman et al.² first described an experimental canine preparation of congestive heart failure produced by chronic rapid ventricular pacing. These investigators demonstrated that pacing dogs at 280 beats/min for 13 to 29 days elevated left ventricular end-diastolic pressure and reduced arterial blood pressure and myocardial force-velocity relations, an index of contractility. Myocardial biopsy samples demonstrated reduced total creatine and phosphocreatine, leading Coleman et al. to speculate that inadequate myocardial oxygen delivery was responsible for the depressed myocardial function. Subsequently, Riegger and Liebau and their colleagues³,⁴ confirmed that pacing dogs for 2 weeks at 240 to 280 beats/min produced elevated pulmonary wedge pressures and reduced cardiac outputs, changes that resolved within 5 days of terminating pacing. The dogs were also shown to exhibit elevated plasma renin, angiotensin II, aldosterone, vasopressin, norepinephrine, and epinephrine levels,³,⁴ as is frequently noted in patients with heart failure.

These observations have established that short-term rapid ventricular pacing in the dog produces a preparation of heart failure similar both hemodynamically and neurohumorally to heart failure in man. However, prior studies provided relatively little information about cardiac changes in this preparation and did not establish whether the preparation could be sustained for a prolonged period. Accordingly, the present study was undertaken (1) to clarify the hemodynamic effects of both short-term (3 weeks) and prolonged (2 months) rapid ventricular pacing, (2) to evaluate the effect of these interventions on cardiac mass and chamber size, (3) to evaluate the effect of pacing on left ventricular wall thickening, (4) to clarify the relative contributions of pacing versus impaired myocardial function to hemodynamic dysfunction in the model, and (5) to assess further the contribution of myocardial ischemia to pacing-induced ventricular dysfunction.

**Hemodynamic effects of chronic rapid ventricular pacing.** Results of the present study confirm that rapid ventricular pacing at 260 beats/min for 3 weeks produces hemodynamic dysfunction resembling biventricular heart failure in man. Specifically, dogs exhibited ascites, reduced arterial blood pressure and cardiac output, and elevated pulmonary wedge and right atrial pressures.

Similar hemodynamic changes have been reported both by Riegger and his colleagues³,⁴ and Coleman et al.² Of interest, however, Coleman et al.² reported an increase rather than a decrease in cardiac output in their paced dogs. One potential reason for this apparent discrepancy is that Coleman et al. obtained hemodynamic measurements after pacing was discontinued,
whereas we obtained most of our measurements in dogs still being paced. However, five dogs in this study were evaluated for 30 min after termination of pacing. All five exhibited persistently reduced cardiac outputs. Nevertheless, it is conceivable that the cardiac output actually increases thereafter. In the three dogs in the present study who were reevaluated 1 week after termination of pacing, cardiac outputs were in fact all higher than during the control study. Presumably, removal of the adverse effects of pacing coupled with increased cardiac preload due to cardiac dilation may result in an augmented cardiac output.

To determine if pacing-induced hemodynamic dysfunction could be sustained for a period longer than 3 weeks, dogs were initially paced at 260 beats/min for a longer period. During pilot studies, this approach usually resulted in progressively more severe fluid retention and the development of anorexia. Most dogs expired at 4 to 6 weeks due to pulmonary edema.

Subsequently, we observed that pacing dogs at low-

![FIGURE 5. Two-dimensional echocardiograms obtained before (left) and immediately after (right) 3 weeks of pacing.](image)

**TABLE 5**

<table>
<thead>
<tr>
<th></th>
<th>Control dogs (n = 6)</th>
<th>Acute pacing (n = 6)</th>
<th>Chronic pacing (n = 5)</th>
<th>Pacer off (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate-pressure product (mm Hg-beats/min)</td>
<td>1527 ± 195</td>
<td>2784 ± 407&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2864 ± 750&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1168 ± 270</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/100 g)</td>
<td>51 ± 32</td>
<td>140 ± 78&lt;sup&gt;b&lt;/sup&gt;</td>
<td>202 ± 141&lt;sup&gt;a&lt;/sup&gt;</td>
<td>126 ± 68</td>
</tr>
<tr>
<td>Myocardial arteriovenous O&lt;sub&gt;2&lt;/sub&gt; difference (ml/dl)</td>
<td>13.3 ± 1.6</td>
<td>12.7 ± 2.0</td>
<td>14.6 ± 1.3</td>
<td>12.1 ± 1.0</td>
</tr>
<tr>
<td>Myocardial VO&lt;sub&gt;2&lt;/sub&gt; (ml/100 g)</td>
<td>6.2 ± 3.6</td>
<td>17.9 ± 10.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40.6 ± 20.0&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>20.9 ± 7.8</td>
</tr>
<tr>
<td>Lactate extraction (%)</td>
<td>40 ± 10</td>
<td>34 ± 10</td>
<td>36 ± 10</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Arterial lactate (mM/l)</td>
<td>2.06 ± 0.92</td>
<td>2.09 ± 0.73</td>
<td>1.94 ± 0.82</td>
<td>2.23 ± 1.08</td>
</tr>
<tr>
<td>Coronary sinus lactate (mM/l)</td>
<td>1.22 ± 0.58</td>
<td>1.42 ± 0.58</td>
<td>1.19 ± 0.46</td>
<td>1.33 ± 0.71</td>
</tr>
</tbody>
</table>

<sup>a</sup>p < .05 vs control; <sup>b</sup>p < .01 vs control; <sup>c</sup>p < .05 vs acute pacing.
er rates (220 to 240 beats/min) also resulted in heart failure, but of a degree that could be readily sustained for 2 months. Therefore, dogs in the present study were paced at rates in this range. At the end of 2 months, the level of fluid retention was usually more than at 3 weeks. Intracardiac diastolic pressures were elevated and cardiac outputs were reduced to a degree similar to that noted at 3 weeks. However, mean arterial pressure tended to be greater than in dogs paced at 260 beats/min for 3 weeks, probably due to the lower pacing rate.

These findings demonstrate that moderate biventricular heart failure can be maintained over prolonged periods with the use of rapid ventricular pacing at rates of 220 to 240. It is likely that more severe heart failure could also be maintained if dogs were paced at 260 beats/min and treated with diuretics to prevent pulmonary edema.

Cardiac morphologic and functional effects of rapid ventricular pacing. The development of hemodynamic abnormalities in the pacing preparation appears to be due initially to an adverse effect of pacing; in this study, pacing produced an immediate decrease in cardiac output and elevation in intracardiac filling pressures. Over time, however, pump dysfunction is exacerbated by development of severe left ventricular dysfunction; ventricular pacing at 260 beats/min was accompanied by a striking impairment of left ventricular wall thickening in the anterior, posterior, and lateral walls. Only the septum appeared to continue contracting normally. Serial studies suggested that this reduction in wall function developed within 1 to 2 weeks of the onset of pacing. In a preliminary report, Armstrong and Stoppes also reported reduced left ventricular ejection fractions in nine dogs paced for 5 ± 1.8 weeks and assessed by two-dimensional echocardiography.

This impaired cardiac function was accompanied by left and right ventricular dilation. At postmortem examination of both dogs paced for 3 weeks and those paced for 2 months, right and left ventricular volumes were noted to be over twice as great as in control dogs. Left ventricular diastolic dimension by M mode echocardiography was also significantly increased in the dogs paced for 3 weeks, confirming that cardiac dilation was present in vivo. In the three dogs that were monitored serially over 3 weeks, significant dilation occurred by 2 weeks and increased further over the third week.

Changes in cardiac volume may occur simply as a result of remodeling of the cardiac chamber with slippage of parallel fibers with respect to each other. Alternatively, chamber dilation can occur due to addition of sarcomeres in series, resulting in cardiac hypertrophy.

In the present study, changes in left ventricular volume appeared to occur in the absence of significant cardiac hypertrophy; comparison of postmortem left ventricular weights in control dogs and dogs paced for either 3 weeks or 2 months demonstrated no significant differences among the three groups. Instead, thinning of the wall occurred in conjunction with chamber dilation.

Current evidence suggests that left ventricular hypertrophy is primarily stimulated by an increase in myocardial systolic wall stress and that hypertropy continues until wall stress is normalized by the consequent increase in wall thickness. Ventricular pacing produced left ventricular dilation, an effect that should augment systolic wall stress. However, arterial pressure was reduced, an effect that should decrease wall stress. These two directionally opposite influences may have cancelled one another, leaving wall stress relatively normal.

In contrast to the absence of left ventricular hypertrophy, approximately a 20% increase in right ventricular free wall mass was noted both at 3 weeks and 2 months. Presumably, right ventricular dilation and increased pulmonary arterial pressure stimulated this hypertrophy; whereas systolic pressures in the left ventricle decreased, right ventricular systolic pressure increased.

Mechanism responsible for pacing-induced depression of left ventricular wall thickening. In their original study of the pacing preparation of heart failure, Coleman et al. demonstrated that left ventricular myocardial stores of creatine and phosphocreatine were significantly depressed in dogs paced for 2 to 4 weeks. These investigators therefore postulated that left ventricular dysfunction in this preparation may be due to an imbalance between myocardial energy production and utilization.

Such an imbalance could alter ventricular function by producing myocardial infarction and/or chronic myocardial ischemia. To exclude myocardial infarction as a factor, we examined the histology of muscle taken from the posterior left ventricular wall, the region that became most dysfunctional with pacing. We also examined the capacity of this region to recover function. Histologic examination failed to demonstrate any evidence of infarction, while serial echocardiographic studies demonstrated that posterior wall function recovered by 2 to 4 days after termination of pacing. Therefore, it seems extremely unlikely that chronic pacing impairs left ventricular function by causing myocardial infarction.
To investigate the contribution of myocardial ischemia to pacing-induced ventricular dysfunction, we measured myocardial blood flow, arteriovenous oxygen difference, and lactate extraction before pacing, immediately after the onset of pacing, at 3 weeks of pacing, and again after termination of pacing. We postulated that, if myocardial ischemia was responsible for the pacing-induced ventricular dysfunction, we should observe myocardial lactate release and an increase in myocardial oxygen extraction.

During acute pacing to 260 beats/min, we found no evidence of ischemia; myocardial lactate and O₂ extraction both remained stable while myocardial flow increased. Chronic pacing was associated with persistently elevated coronary blood flow, but again with no significant change in myocardial lactate and O₂ extraction.

These findings suggest that ischemia is not responsible for pacing-induced ventricular dysfunction. In actuality, the metabolic observations made by Coleman et al. also do not necessarily indicate ischemia. Myocardial phosphocreatine concentration is sensitive to changes in myocardial demand in the presence of adequate O₂ delivery. Therefore, the modestly reduced phosphocreatine levels observed by these investigators in paced dogs could be due to increased myocardial O₂ demand alone. The reduced creatine levels noted by Coleman et al. also may be due to chronically increased myocardial demand. For example, Pool et al. noted that right ventricular phosphocreatine and creatine levels were reduced in cats with right ventricular hypertrophy due to pulmonary arterial banding.

What is responsible for the pacing-induced reduction in myocardial wall thickening? This study does not afford an answer to this question, although an abnormality of calcium metabolism and/or myocardial ATPase activity seems the most likely mechanism.

Technical limitations. There are several limitations of the methods used in the present study that should be recognized. Postmortem volume changes were evaluated in hearts arrested in diastole. However, the hearts were not distended to physiologic end-diastolic pressures and therefore cardiac volume in vivo was underestimated. However, hearts from both control and paced dogs were treated similarly, and echocardiographic measurements confirmed cardiac dilation in vivo.

The echocardiographic measurements also have certain limitations. Only one section through the left ventricle was evaluated. Therefore, characteristics of other areas of the heart remain unknown. Left ventricular ejection fractions were not determined due to difficulties with obtaining left ventricular apical views in awake, upright dogs and concerns with the validity of making such measurements in ventricles with marked regional wall motion abnormalities.

Finally, it should be noted that use of myocardial lactate extraction as an index of ischemia has limitations. Since the heart normally extracts lactate, release of lactate from small areas may be obscured by the continuing large extraction by the rest of the myocardium. Furthermore, under conditions of severe ischemia, glycolysis is inhibited. However, these phenomena are not likely to have confounded the results of the present study, since the extent of left ventricle dysfunction was large and, if severe ischemia had been present, it is unlikely that dogs would have survived.

Implications. The findings of the present study suggest that rapid ventricular pacing in the dog produces a useful experimental preparation of chronic low-output, edematous heart failure. This preparation exhibits hemodynamic and neurohumoral abnormalities closely resembling heart failure in man. Therefore, it should be useful both for studying the mechanisms underlying circulatory and neurohumoral changes in human heart failure and for studying the effect of pharmacologic agents. Particular advantages of this preparation over others are that it is a technically simple one to produce and that it exhibits biventricular heart failure. Other preparations are technically more complicated to produce and, in general, result in pump dysfunction of only the right or left ventricle. Severe dysfunction of the left ventricle has been particularly difficult to produce with other preparations; prior methods used to damage the left ventricle frequently produce either too little damage or high early mortality due to damage that is too extensive.

Other attractive features of this pacing preparation include development of reversible cardiac chamber dilation and altered wall thickening. It therefore may be useful for studying the mechanism responsible for changes in cardiac shape and size accompanying heart failure and for investigating regulation of myocardial contractility.

The principal limitations of this preparation are threefold. Ventricular pacing is required to sustain the preparation, an intervention that may have effects on the circulation independent of those produced by heart failure. Second, the method of producing cardiac dysfunction is different from the mechanisms that produce cardiac dysfunction in man. Third, wall thickening is impaired asymmetrically. Therefore, for certain purposes, the pacing preparation may not be suitable. Nevertheless, it should be extremely useful in the in-
vestigation of areas in which the type of cardiac damage is probably relatively unimportant, such as the effect of heart failure on the peripheral circulation.

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