Evaluation of Ventricular Contractility Indexes in the Dog With Left Ventricular Dysfunction Induced by Rapid Atrial Pacing

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Eight dogs were studied by simultaneous invasive hemodynamic and two-dimensional echocardiographic methods to determine whether left ventricular contractility is altered by 2 weeks of rapid atrial pacing. Additionally, this study evaluated the response of three ventricular contractility indexes to both the pacing intervention and acute load alteration. The indexes compared were ejection fraction, peak systolic pressure to end-systolic volume index ratio (SBP/ESVI) and end-systolic wall stress to end-systolic volume index ratio (ESWS/ESVI).

After 2 weeks of pacing at 265 ± 20 min⁻¹ (mean ± SD), cardiac index and ejection fraction were reduced to 73 ± 38 ml/kg per min and 22 ± 6%, respectively, from 161 ± 22 and 46 ± 7 before pacing (both p < 0.001). Concomitantly, SBP/ESVI and ESWS/ESVI were reduced to 34 ± 10 mm Hg/ml per kg and 54 ± 19 g/cm² per ml per kg, respectively, from 84 ± 29 and 121 ± 36 before pacing (both p < 0.005). There were high correlations for the changes in SBP/ESVI and ejection fraction (r = 0.94, p < 0.001) and ESWS/ESVI and ejection fraction (r = 0.89, p < 0.003). Acute afterload alteration with phenylephrine depressed ejection fraction but not SBP/ESVI or ESWS/ESVI.

Therefore, this study demonstrates 1) that left ventricular contractility is markedly depressed in the dog by 2 weeks of rapid atrial pacing, and 2) that SBP/ESVI and ESWS/ESVI are superior to ejection fraction as ventricular contractility indexes because these ratios accurately measure contractility changes but are influenced less by afterload conditions.

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tractility in conditions such as chronic mitral regurgitation. For this reason, indexes that are independent of or take load conditions into account are more desirable measures of ventricular contractility (10).

Suga and Sagawa (11) have demonstrated in the dog that the ventricular end-systolic pressure-volume relation is insensitive to preload and afterload, and that the linear slope of this relation can be used to define ventricular contractility. Others (12) have shown the usefulness of the linear end-systolic wall stress-volume relation in measuring contractility. However, these relations are not easily applied in the clinical setting because of the need for simultaneous pressure and volume measurements over a wide range of loading conditions.

The peak systolic pressure to end-systolic volume index ratio (SBP/ESVI) and the end-systolic wall stress to end-systolic volume index ratio (ESWS/ESVI) have been proposed as simplified estimates of the slope of linear pressure-volume and stress-volume relations. However, these are controversial simplifications (10) and further studies are necessary to validate the use of these two indexes to assess changes in ventricular contractile state.

This report describes the deterioration in left ventricular contractility caused by 2 weeks of rapid atrial pacing in the dog, and demonstrates how closely changes in SBP/ESVI and ESWS/ESVI reflect changes in ejection fraction. Additionally, it shows that SBP/ESVI and ESWS/ESVI are affected less by afterload changes than is ejection fraction.

**Methods**

This study was performed in accordance with the guidelines of the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984 by the American Heart Association.

**Pacemaker implantation.** Ten male dogs (16 to 25 kg) had a permanent pacemaker generator and an atrial epicardial lead surgically implanted ≥1 week before study. A thoracotomy was performed through the left fourth interspace, under pentobarbital anesthesia (25 mg/kg body weight), to attach a Medtronic pacing lead to the left atrial appendage. The lead was then tunneled to a Medtronic Spectrax generator located in a surgical pocket between the scapulae. After a brief test of the pacing system, it was turned off while the animal recovered for 7 days.

**Experimental protocol.** Two-dimensional echocardiography was performed immediately before and after 2 weeks of pacing, in conjunction with a simultaneous invasive hemodynamic study. These combined studies were obtained in the anesthetized dog, in which anesthesia was induced with sodium thiopental (15 mg/kg) and maintained by a halothane/oxygen mixture (1.5% halothane) at 2 liters/min. Ventilation was maintained by a constant volume ventilator (Fraser Harlake model 701). Additional echocardiograms were acquired, without a hemodynamic study, before study entry and at 2 weeks after termination of pacing. For these two studies the dog was evaluated in the conscious state while standing.

Ventricular loading conditions were altered abruptly in the simultaneous hemodynamic and echocardiographic studies and data were collected during three different load states. Baseline (load state 1) data were collected 15 to 20 min after induction of anesthesia to ensure hemodynamic stability. Preload augmentation (load state 2) was accomplished by intravenous infusion of normal saline solution at 50 ml/min (total 300 to 450 ml). Afterload augmentation (load state 3) was induced by intravenous phenylephrine infusion over 3 to 5 min to increase systolic blood pressure by 25% to 30%. The infusion rate was 1.3 μg/kg per min titrating to accomplish the desired effect.

Rapid atrial pacing was not begun until the end of the first hemodynamic study. A Medtronic (model 9701E CEN-SYS) pacemaker programmer was used to set the pacing rate at 280 min⁻¹. If the dog failed to maintain 1:1 AV conduction, a lower rate was used to enable consistent 1:1 conduction. The effective pacing rate was checked at 1, 7 and 14 days. Pacing was discontinued ≤1 h before the second invasive hemodynamic evaluation.

**Hemodynamic assessment.** Femoral artery pressure was monitored with use of an arterial line setup, introduced percutaneously into the artery. Right atrial and pulmonary artery pressures were monitored through a 7F Swan-Ganz thermodilution catheter, introduced percutaneously into the right external jugular vein. All pressures were recorded with a four-channel pressure recorder (Hewlett-Packard model 78353 patient monitor). The dog was maintained in a left lateral position throughout the study, and zero reference of pressure manometers was set at left atrial level.

The following pressures were recorded: mean right atrial pressure (RAP), mean pulmonary capillary wedge pressure, and peak systolic and mean (MAP) femoral artery pressures.

**Thermol dilution cardiac output results** were averaged from 3 to 5 right atrial injections (5 ml aliquots) of iced 0.9% saline solution. Thermol dilution curves were integrated with use of an American Edwards Laboratory (model 9520A) cardiac output computer. Cardiac index was derived by normalizing cardiac output to body weight in kilograms. Systemic vascular resistance was derived by the formula 80 × (MAP – RAP)/cardiac output.

**Echocardiographic assessment.** Two-dimensional echocardiograms were recorded with use of a Diasonics Cardiovue 100 Imaging System with a 3.5 or 5 MHz transducer. Left ventricular images were obtained from the two-chamber long-axis plane and the short-axis plane (mid-papillary muscle level) by a transthoracic approach from the dog's right side.

Echocardiographic images were recorded on videotape for subsequent quantitative analysis with use of a Microson-
animals were able to maintain 1:1 AV conduction at an atrial
ascites, pleural effusion or change in body weight. Not all
none of these eight dogs displayed pulmonary edema,
ately before and after 14 ± 1 days of rapid atrial pacing.
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severe congestive heart failure with frank pulmonary edema,
died because of intractable ventricular fibrillation (during
and thus were excluded from the analysis. One of these dogs
at the end of 14 days of pacing, precluding a follow-up study
squares method.
lation and regression analysis was done by the linear least
was considered indicative of a significant difference. Corre-
was used as its own control, and a probability value of <0.05
Duncan Multiple Range Test) when continuous. Each dog
variable was discrete, or analysis of variance (ANOVA,
use of the Student's paired t-test (two-tailed) when the
pressure.
Femoral artery pressure was substituted for ventricular
posterior wall thickness and L is the long-axis length.
where P is pressure, D is short-axis diameter, PWT is
thickness was measured at this point on the posterior wall.
Left ventricular circumferential wall stress was derived
with use of the following equation (14):
Wall stress = \( \frac{P \times D}{2PWT} \times \left[ 1 - \frac{(D^2)}{2L^2} \right] \),
where P is pressure, D is short-axis diameter, PWT is
posterior wall thickness and L is the long-axis length.
Femoral artery pressure was substituted for ventricular
pressure.

Statistical analysis. Study variables were analyzed with
use of the Student's paired t-test (two-tailed) when the
variable was discrete, or analysis of variance (ANOVA,
Duncan Multiple Range Test) when continuous. Each dog
was used as its own control, and a probability value of <0.05
was considered indicative of a significant difference. Corre-
lational analysis was done by the linear least squares method.

Results

Protocol completion. Two of the 10 animals died suddenly
at the end of 14 days of pacing, precluding a follow-up study
and thus were excluded from the analysis. One of these dogs
died because of intractable ventricular fibrillation (during
induction of anesthesia), and the other collapsed and was
found pulseless in the holding facility. Both dogs displayed
severe congestive heart failure with frank pulmonary edema,
ascites and pleural effusions.
The remaining eight dogs had complete studies immedi-
ately before and after 14 ± 1 days of rapid atrial pacing.
None of these eight dogs displayed pulmonary edema,
ascites, pleural effusion or change in body weight. Not all
animals were able to maintain 1:1 AV conduction at an atrial
pacing rate of 280 min⁻¹. The range of pacing rates was 230
to 280 min⁻¹ with an average (± SD) of 265 ± 20 and a
median rate of 273.

Effect of pacing on left ventricular function. Table I
displays the change in hemodynamic and echocardiographic
variables from the pre-pacing study to the repeat assessment
± 1 h after termination of the pacing. There was 1) a
significant increase in the average heart rate, mean pulmo-
mary capillary wedge pressure and mean right atrial pressure;
2) a decrease in peak systolic and mean femoral artery
pressure (although not statistically significant); 3) a rise in
systemic vascular resistance; and 4) an average decline in
cardiac index of 55%. Thus, the dogs displayed a low cardiac
output state after pacing.

Left ventricular end-diastolic and end-systolic volumes
were increased at this time compared with those before
pacing. The increase in end-systolic volume (94%) was
significantly greater (p < 0.001) than the increase in end-
diastolic volume (40%) and, as a result, ejection fraction was
reduced by an average of 5%. End-systolic wall stress
(ESWS) was not significantly altered after pacing, despite
the increase in end-systolic volume index (ESVI), because
peak systolic blood pressure (SBP) tended to decrease with
only a small decline in end-systolic wall thickness.

Comparative effect of pacing on contractility indexes (Fig.
1). After pacing, the average decline in ejection fraction was
52%, whereas SBP/ESVI and ESWS/ESVI displayed reduc-
tions of 60% and 54%, respectively. Thus, the three contrac-
tility indexes were decreased to a similar degree by the
pacing intervention. When the pacing-induced changes in

### Table 1. Comparison of Hemodynamic and Left Ventricular
Echocardiographic Measurements Before and After 2 Weeks of
Rapid Atrial Pacing in Eight Dogs

<table>
<thead>
<tr>
<th></th>
<th>Pre-pacing</th>
<th>Post-pacing</th>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>21.4 ± 3.1</td>
<td>21.8 ± 3.2</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>126 ± 15</td>
<td>137 ± 13*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8 ± 2</td>
<td>14 ± 5*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>2 ± 0.8</td>
<td>6 ± 4*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120 ± 11</td>
<td>98 ± 23</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>93 ± 13</td>
<td>77 ± 20</td>
</tr>
<tr>
<td>SVR (dynes/cm²)</td>
<td>2,155 ± 196</td>
<td>3,951 ± 793*</td>
</tr>
<tr>
<td>CI (ml/kg per min)</td>
<td>161 ± 22</td>
<td>73 ± 38*</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>59 ± 10</td>
<td>82 ± 13*</td>
</tr>
<tr>
<td>ESVI (ml/kg)</td>
<td>1.7 ± 0.6</td>
<td>3.0 ± 0.6*</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>10.0 ± 1.3</td>
<td>9.2 ± 0.7</td>
</tr>
<tr>
<td>PWTS (mm)</td>
<td>11.9 ± 1.2</td>
<td>10.5 ± 1.0*</td>
</tr>
<tr>
<td>ESWS (g/cm²)</td>
<td>175 ± 26</td>
<td>157 ± 50</td>
</tr>
</tbody>
</table>

*p < 0.05: t* p < 0.001. Data are mean values ± SD. CI = cardiac index;
EDV = end-diastolic volume; ESV = end-systolic volume; ESVI = end-
systolic volume index; ESWS = end-systolic wall stress; MAP = mean
arterial pressure; PCWP = mean pulmonary capillary wedge pressure; PWTd
= posterior wall thickness at end-diastole; PWTS = posterior wall thickness at
end-systole; RAP = mean right atrial pressure; SBP = peak-systolic pressure;
SVR = systemic vascular resistance.
SBP/ESVI, ESWS/ESVI and ejection fraction were compared (Fig. 2 to 4), very high correlations were seen for changes in SBP/ESVI versus ejection fraction ($r = 0.94$), ESWS/ESVI versus ejection fraction ($r = 0.89$) and SBP/ESVI versus ESWS/ESVI ($r = 0.95$).

**Comparative effect of short-term load alteration on contractility indexes (Table 2).** In each of the two hemodynamic studies, volume loading created an increase in left ventricular filling pressure without a change in heart rate, peak systolic pressure or end-systolic wall stress (compared with baseline). The increase in filling pressure achieved significance only in the pre-pacing study, where it increased from 8 to 12 mm Hg. This degree of volume loading did not alter ejection fraction, SBP/ESVI or ESWS/ESVI.

In the pre-pacing study, phenylephrine administration caused a significant increase in peak systolic pressure, end-systolic wall stress and pulmonary wedge pressure (compared with both baseline and volume loading). As a result of the abrupt increase in afterload, ejection fraction was reduced; however, SBP/ESVI and ESWS/ESVI were both unchanged.

In the post-pacing study, phenylephrine increased pulmonary wedge pressure, but the respective increases in peak systolic pressure and end-systolic wall stress did not achieve significance. In the context of this response to phenylephrine, SBP/ESVI, ESWS/ESVI and ejection fraction were unchanged.

**Ventricular function 2 weeks after termination of pacing** (Table 3). The eight dogs were observed for 2 weeks beyond the termination of pacing. At that time, echocardiograms performed in the conscious animal revealed that the average ejection fraction ($\pm$SD) was $58 \pm 12\%$. Five dogs had an echocardiogram performed in the conscious state before study entry, and in these dogs ejection fraction had returned to pre-study levels by 2 weeks after termination of pacing.
However, the end-diastolic and end-systolic volumes were still slightly elevated.

**Discussion**

This study was designed to evaluate the effect of long-term rapid atrial pacing on left ventricular systolic function in the dog, and to evaluate the effects of both the pacing intervention and abrupt load alteration on ejection fraction, peak systolic pressure to end-systolic volume index ratio (SBP/ESVI) and end-systolic wall stress to end-systolic volume index ratio (ESWS/ESVI).

**Pacing-induced depression of left ventricular function.** Rapid atrial pacing caused a marked decline in cardiac index and a 94% rise in end-systolic volume without a significant change in ventricular afterload (end-systolic wall stress). These changes strongly suggest that left ventricular contractility was decreased; supporting this view were the marked reductions in ejection fraction, SBP/ESVI and ESWS/ESVI. The pacing-induced decline in ejection fraction, SBP/ESVI and ESWS/ESVI far exceeded any reduction that occurred with short-term load perturbation.

*End-systolic wall stress* was used as the standard measure of ventricular afterload in this study because it reflects the combined effects of peripheral loading conditions and left ventricular pressure, dimension and wall thickness. Therefore, it is a more reliable index of afterload than is systemic vascular resistance (15). Systemic vascular resistance was increased after pacing; however, we, like other investigators (15), have found that this increase did not reflect the change in end-systolic wall stress.

Ejection fraction returned to normal weeks after termination of pacing, indicating that the deterioration in left ventricular contractility was reversible.

**Similarity of this model to other models of cardiac dysfunction.** The similarities between the current model of ventricular dysfunction and that created in the dog by ventricular pacing at similar rates (2–6) are 1) the hemodynamic manifestations of ventricular dysfunction, 2) the time required to develop left ventricular dysfunction, 3) the reversible nature of the dysfunction, and 4) the time frame of recovery.

The advantage of using rapid atrial pacing rather than rapid ventricular pacing to induce ventricular dysfunction is that similar results can be achieved without the need for direct ventricular stimulation. This approach avoids the loss of AV synchrony, the abnormal sequence of ventricular contraction (and relaxation) and AV valve regurgitation, all of which may be important if the model is used to study ventricular mechanical function.
Comparison of contractility indexes. Clinical studies (16-21) comparing the end-systolic pressure/volume or stress/volume ratios with ejection fraction have suggested that the simple ratios are superior indexes of ventricular contractility because a measure of afterload is incorporated. However, there is controversy over how useful these ratios are for evaluating short- or long-term changes in inotropic state (10). We have addressed this issue by comparing SBP/ESVI and ESWS/ESVI with ejection fraction in the dog with induced left ventricular contractile dysfunction.

We observed that the pacing-induced reductions in SBP/ESVI, ESWS/ESVI and ejection fraction were remarkably similar, and that changes in each variable correlated strongly with changes in the others. This observation implies that the sensitivity of these respective indexes to a deterioration in left ventricular contractility is similar. The important difference, however, is that SBP/ESVI and ESWS/ESVI were not depressed by a phenylephrine-induced rise in afterload, whereas ejection fraction was. This disparity was seen primarily in the pre-pacing study. There appeared to be a blunted effect of phenylephrine on afterload in the post-pacing study. Such a diminished effect of phenylephrine on afterload had been described in dogs with ventricular failure induced by rapid ventricular pacing (22).

The strong correlation between the change in SBP/ESVI and ESWS/ESVI (with depressed contractility) indicates that peak systolic pressure is a suitable substitute for end-systolic wall stress in the ratio, simplifying the measurement of contractility in the clinical setting. These findings demonstrate the usefulness of SBP/ESVI and ESWS/ESVI to measure long-term changes in contractile state, and strongly suggest that these ratios are superior to ejection fraction because of reduced afterload sensitivity.

Possible mechanisms of altered cardiovascular function. This initial study did not attempt to define the biochemical mechanism by which ventricular dysfunction occurred or the hormonal derangements accompanying ventricular dysfunction. However, the common features of the current model and those of rapid ventricular pacing suggest that the pathway to ventricular dysfunction may be the same.

An early report (2) noted depletion of myocardial high energy phosphates and creatine with the creation of ventricular dysfunction by rapid ventricular pacing. More recently, a reduction in myocardial norepinephrine and calcium adenosine triphosphatase (ATPase) has been shown to occur with ventricular pacing-induced heart failure (23). Additionally, alterations in plasma levels of renin, angiotensin II, aldosterone, norepinephrine, epinephrine and atrial natriuretic peptide have been noted and are believed to contribute to the manifestations of heart failure in that model (3,6). Baroreceptor sensitivity (to phenylephrine) is also altered when heart failure occurs in that model (22), and this effect may explain why we saw less of a rise in afterload with phenylephrine after pacing compared with that before pacing.

Limitations of the study. Our study did not include assessment of biochemical or hormonal variables that might have added additional important information. Halothane anesthesia may have contributed to the depression of ventricular contractility after pacing; however, it was not the primary cause of the altered contractility because the post-pacing anesthesia protocol was identical to that used before pacing. Furthermore, any effect of anesthesia should not have influenced the comparison of contractility indexes obtained simultaneously. Phenylephrine administration (to augment afterload) may have also caused inotropic stimulation. However, ejection fraction was decreased, not increased, with phenylephrine administration.

Femoral artery pressure was substituted for ventricular pressure in the measurement of end-systolic wall stress. This substitution was made because the former pressure is easier to obtain and is possibly more analogous to sphygmomanometer cuff pressures (used in clinical studies). An excellent correlation (r = 0.89) has been shown between systolic pressure by cuff measurement and that by high fidelity catheters in the left ventricle (24).

Clinical implications. This study confirms that a supraventricular tachycardia (in this case rapid atrial pacing) can cause a reversible form of ventricular dysfunction, as suggested by clinical reports (7-9). However, this confirmation does not imply that the ventricular dysfunction described herein is the same as that seen in the clinical setting.

The most clinically relevant aspect of this study is the usefulness of the model to conduct studies of ventricular mechanical function. To our knowledge, this study is the first to systematically compare the responses of ejection fraction, SBP/ESVI and ESWS/ESVI to both a chronic depression in left ventricular contractility and acute load alteration. We have demonstrated that ejection fraction, SBP/ESVI and ESWS/ESVI are all useful indexes to measure chronic changes in ventricular contractility. However, because SBP/ESVI and ESWS/ESVI are affected less by afterload changes, these are more desirable indexes of contractility than is ejection fraction.

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References
4. Armstrong PW, Stopps TP, Ford SE, De Bold AJ. Rapid ventricular


