# Usefulness of dobutamine stress tests for detection of cardiac abnormalities in dogs with experimentally induced early left ventricular dysfunction

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**Objective**—To determine whether dobutamine stress tests (DST) can be used to detect cardiac dysfunction in dogs with early left ventricular dysfunction (ELVD) induced by rapid right ventricular pacing (RRVP).

**Animals**—7 adult male Beagles.

**Procedure**—A pacemaker was surgically implanted in each dog at the level of the right ventricular apex. Electrocardiography, Doppler sphygmomanometry, and Doppler echocardiography were performed before and during a DST prior to activation of the pacemaker and every 3 to 4 days during the period of RRVP. Dobutamine stress tests were performed by infusing dobutamine at incremental dosages ranging from 12.5 to 42.5 µg/kg of body weight/min.

**Results**—Clinical signs of congestive heart failure were not observed during the pacing period. However, all dogs developed ELVD associated with significant changes in values for most Doppler echocardiographic variables obtained prior to DST. Adverse cardiac effects were not detected during DST. Most Doppler echocardiographic indices of cardiac function were significantly altered in response to dobutamine infusion during the pacing period, compared with prepacing values. However, a dobutamine-induced 2-fold increase in cardiac output was maintained.

**Conclusions and Clinical Relevance**—Dobutamine stress tests can be safely performed in dogs with experimentally induced ELVD. Dobutamine stress tests may be a sensitive, noninvasive diagnostic method, complementary to standard clinical examinations, for detection of early cardiac dysfunction in dogs asymptomatic for dilated cardiomyopathy. (*Am J Vet Res* 2001;62:448–455)

**Dilated cardiomyopathy (DCM)** in dogs is a chronic myocardial disease defined by a progressive decrease in myocardial contractility generally associated with an increase in chamber size.[1] Since the advent of echocardiography, clinical signs of congestive heart failure together with detection of myocardial hypokinesis and left ventricular dilatation are considered diagnostic of DCM in dogs.[1-4] However, diagnosis of DCM in dogs without clinical signs of cardiac abnormalities remains difficult. Paroxysmal arrhythmias or echocardiographic evidence of left ventricular dilatation and hypokinesis in the absence of clinical signs attributable to heart disease are the most commonly accepted diagnostic criteria for DCM in such dogs.[5] However, results of resting echocardiography for healthy and affected dogs often overlap.[5] Moreover, in some dogs with low fractional shortening values and evidence of left ventricular dilatation during initial examination, values are within reference range during subsequent examinations.[6] Detection of attenuated wavy fibers on histologic examination of myocardium is highly specific and sensitive for detection of DCM. Such fibers can be detected in the early stages of DCM, prior to development of clinical and echocardiographic signs of the disease. However, diagnosis of DCM on the basis of attenuated wavy fibers can only be made postmortem.[7]

Exercise- and pharmacologic-based cardiac stress tests have been developed for use in human medicine. **Dobutamine stress tests (DST)** have been reported to be an accurate and noninvasive diagnostic technique for detection of cardiac dysfunction in asymptomatic patients with 1 of several cardiac diseases.[8-10] Therefore, DST may provide a reliable and noninvasive method to assess cardiac function in dogs suspected of having DCM. Recently, a weak inotropic challenge with dobutamine was shown to be a safe and clinically applicable screening test for detection of early DCM in Doberman Pinschers. However, results of this test were not clearly superior to results of resting echocardiography.[11] Therefore, the purpose of the study reported here was to determine whether administration of increasing dosages of dobutamine would allow for detection of myocardial dysfunction in dogs with experimentally **induced early left ventricular dysfunction (ELVD)**, a condition that closely mimics early DCM in dogs.

## Materials and Methods

**Animals**—Seven 4- to 5-year-old male Beagles, weighing between 13 and 19 kg, were used in this study. Dogs were housed under standard conditions, fed dry dog food once daily, given access to water ad libitum, and walked regularly. They were observed daily, acclimated to the laboratory environment, and trained to lie quietly in lateral recumbency for

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up to 1 hour. The experimental protocol was approved by the Institutional National Animal Care and Use Committee.

**Placement of cardiac pacemaker**—Dogs were sedated with acepromazine (0.04 mg/kg of body weight, IV) and methadone (0.4 mg/kg, IV). Anesthesia was induced with thiopental (10 mg/kg to effect, IV) and maintained with isoflurane in oxygen delivered via positive pressure ventilation. After incision of the skin and blunt dissection of the right external jugular vein, a bipolar pacemaker lead[a] was advanced, under fluoroscopic guidance, into the vein to the level of the right ventricular apex. The attachment of the lead was confirmed by measuring the threshold potential required to electrically stimulate the myocardium. The lead was connected to a multiprogrammable pulse generator[b] inserted into a small subcutaneous pocket created in the cervical region. After implantation, the pacemaker was programmed at a rate of 30 pulses/min in the inhibited mode. Incisions were sutured, and a bandage was applied to the neck. Cephalexin (20 mg/kg, SC, q 12 h) was administered for 7 days after surgery. The dogs were allowed to recover for 14 to 21 days.

**Experimental design**—Dogs were handled daily to verify food and water intake. Physical examinations and ECG were performed every day during the recovery period to ensure proper operation of the pacemaker. At the end of the recovery period (day 0; baseline), physical examinations (cardiac and pulmonary auscultation and determination of body weight, mentation, attitude, rectal temperature, color of mucous membranes, capillary refill time, pulse pressure, and heart and respiratory rates), 6-lead ECG, thoracic radiography, Doppler sphygmomanometry, and Doppler echocardiography were performed before DST. Immediately after predobutamine echocardiography, DST were performed. **Rapid right ventricular pacing (RRVP)** was then initiated by activating pacemakers at 180 beats/min for 10 days followed by 215 beats/min for 7 to 15 days (pacing period). During the pacing period, dogs were examined every 3 to 4 days according to the protocol followed on day 0. All examinations were performed with the dogs in sinus rhythm after deactivation of the pacemaker and a 30-minute stabilization period.

Three stages of ELVD were defined on the basis of results of predobutamine echocardiography. **Fractional shortening of the left ventricle (%FS)** > 28% and a < 10% increase in **left ventricular internal diameter at end diastole (LVIDd)** relative to baseline values was defined as stage 1. Stage 2 was defined as %FS < 28% and a < 10% increase in LVIDd, whereas stage 3 was defined as %FS < 28% and a > 10% increase in LVIDd. Once stage-3 ELVD was diagnosed, the pacemaker was deactivated and surgically removed.

**Radiography**—Ventrodorsal and right lateral radiographic views of the thorax were obtained at peak inspiration. Cardiac volume (ie, sum of the lengths of long and short axes) was quantitatively assessed according to the method described by Buchanan and Bücheler.[12] Pulmonary features were described qualitatively.

**Determination of blood pressure**—**Systolic arterial blood pressure (SABP)** was assessed by use of Doppler sphygmomanometry.[c] Dogs were positioned in right lateral recumbency, a flat infant-sized Doppler probe was placed over the common digital branch of the left radial artery, and an infant-sized blood pressure monitoring cuff was placed midway between the olecranon and carpus. Three independent measurements were recorded, and the mean was determined.

**Doppler echocardiography**—Doppler echocardiography was performed, using electronic ultrasound scanner equipment[d] with a 5-MHz phased array probe[e] for bidimensional and M-mode measurements and a 2.5-MHz probe[f] for Doppler measurements. Recordings were registered at a rate of 50 mm/s for dimensional variables and 100 mm/s for time and Doppler variables. Selected data were recorded on videotape for off-line measurements and calculations. A bipolar ECG was recorded on line and a 6-lead ECG was recorded on paper. Systolic arterial blood pressure was assessed during echocardiography by use of Doppler sphygmomanometry.

**Dobutamine stress tests**—A catheter was inserted into a cephalic vein to allow infusion of dobutamine. Dogs were positioned in lateral recumbency on a table that allowed the echocardiographic transducer to be manipulated from below. After recording predobutamine echocardiographic and Doppler images, dobutamine (500 µg/ml in 5% dextrose) was infused IV, using a volumetric pump. The initial dosage was 7.5 µg/kg/min. After 5 minutes, the dosage was increased to 12.5 µg/kg/min. Thereafter, at 15-minute intervals, the dosage was increased by 10 µg/kg/min until a maximum dosage of 42.5 µg/kg/min was achieved. At dosages of 12.5 to 42.5 µg/kg/min, echocardiography was again performed. When Doppler echocardiographic recordings were completed, a 6-lead ECG was recorded, and 3 independent measurements of SABP were averaged. Recordings and measurements were made in the same order between the 5th and the 15th minute of each dobutamine infusion dosage. Tests were interrupted when dogs became uncontrollably excited or developed paroxysmal ventricular tachycardia, hypotension (ie, SABP at least 20 mm Hg less than the predobutamine value), or severe hypertension (ie, SABP > 240 mm Hg), or when ST depression detected on the ECG was > 2 mm.

**Echocardiographic measurements**—Doppler echocardiography was performed according to guidelines recommended by the American Society of Echocardiography[13] and the American College of Veterinary Internal Medicine.[14] Left ventricular internal diameter, **interventricular septal thickness (IVS)**, and **left ventricular free wall thickness (LVFW)**, at **end diastole (d)** and **end systole (s)** were measured from the M-mode right short axis view of the left ventricle at the level of the chordae tendinae, and the mean of 3 cardiac cycles was calculated. Fractional shortening of the left ventricle, **fractional thickening of the interventricular septum (%IVS)**, and **fractional thickening of the left ventricular free wall (%LVFW)** were calculated. **End-diastolic left ventricular volume index (EDVI)** and **end-systolic left ventricular volume index (ESVI)** were obtained, using the Teichholz corrected cube formula; **body surface area (BSA)** was calculated, using the following formula:

$$BSA\ (m^2) = 10 \times \text{body weight}\ (g)^{2/3}/10^4$$

**Ejection fraction (%EF)** was calculated, using the following formula:

$$\%EF = (EDVI - ESVI/EDVI) \times 100$$

**Stroke index (SIecho)** was calculated as the difference between EDVI and ESVI. **Cardiac index (CIecho)** was calculated as SIecho multiplied by heart rate.

**Pre-ejection period (PEP)** and **left ventricular ejection time (LVET)** were measured from the M-mode right long axis view of the left ventricular outflow tract, and the mean of 5 to 10 cardiac cycles was calculated. **The ratio of PEP to LVET (PEP/LVET)** was determined, and the **mean velocity of fiber shortening (mVcf)** was calculated, using the following formula :

$$mVcf = (\%FS/LVET) \times 10$$

Internal systolic aortic diameter was measured before dobutamine infusion from the bidimensional right long axis view of the left ventricular outflow tract at the aortic annulus at the site of attachment of the aortic valve leaflets, and the

mean of 3 cardiac cycles was calculated. Aortic area was calculated, assuming a circular shape, and this value was used to calculate **Doppler stroke index (SIdoppler)** and **Doppler cardiac index (CIdoppler)**.

For Doppler examination of pulmonary and aortic flows, the sample volume was positioned at the level of the pulmonary and aortic valves, and signals from the motion of the leaflets were often apparent. For Doppler examination of mitral flow, the sample volume was positioned at the tip of the closed valve. For each valve, positioning was optimized, using the audio signal, to maximize the spectral display of peak velocity of blood flow and to obtain the purest tone. All measurements were performed at the outer edge of velocity spectra. Each Doppler result represented the mean of the 3 to 6 cardiac cycles with maximal peak velocities.

Doppler examination of pulmonary flow was performed from a right axis view of the heart base, which allowed observation of the right ventricular outflow tract and the main pulmonary artery in long axis. **Peak flow velocity (PFV)**, **acceleration time at the pulmonary valve (ATpulmonary)**, and **deceleration time at the pulmonary valve (DTpulmonary)** were measured. The ratio of **ATpulmonary to DTpulmonary (AT/DTpulmonary)** was calculated.

Doppler examination of the aortic flow was performed from the subcostal position. Measurements and calculations were performed as for pulmonary flow. **Velocity time integral (VTIaortic)** was also measured to allow for calculation of SIdoppler and CIdoppler, using the following formulas:

$$\text{SIdoppler} = (\text{VTIaortic} \times \text{aortic area})/\text{BSA}$$
$$\text{CIdoppler} = \text{SIdoppler} \times \text{HR}.$$

Doppler examination of the mitral flow was performed from the left caudal position. **Peak velocity of the mitral E wave (MVE)** and **peak velocity of the mitral A wave (MVA)** were measured. The **ratio of MVE to MVA (mitral E/A)** was calculated. If E and A waves were completely fused at fast heart rates, the wave was measured and arbitrarily reported as an isolated E wave.

**Statistical analyses**—A repeated measures ANOVA was performed according to a 2-way factorial design.[15] The first factor indicated the stage of ELVD (ie, baseline and stages 1, 2, and 3) and the second factor indicated values for each variable before DST and at the 4 dobutamine infusion dosages. Stage of ELVD was considered a grouping factor instead of a repeated measures factor, because stage 1 of ELVD was not diagnosed in 1 dog, and more than 1 DST was performed in other dogs at the same stage of ELVD.

To determine the dobutamine infusion dosage at which significant differences in values were detected, an ANOVA was used to compare values obtained at consecutive infusion dosages. To emphasize the interaction between the 2 factors when significant, **maximal percentage change (MPC)** at each stage of ELVD was calculated for the relevant variables as follows:

$$\text{MPC} = (\text{value at } 42.5\ \mu\text{g/kg/min} - \text{value at } 0\ \mu\text{g/kg/min})/\text{value at } 0\ \mu\text{g/kg/min}$$

For each of these variables, MPC at different stages of ELVD were compared by use of a 1-way ANOVA, and when $P \leq 0.05$, values at stages 1, 2, and 3 were compared with values at stage 0. For all analyses, significance was set at $P \leq 0.05$.

Table 1—Mean (± SEM) values for echocardiographic and Doppler indices of left ventricular function and morphology determined for 7 male Beagles before (baseline) and after development of pacing-induced early left ventricular dysfunction (ELVD)

| | | ELVD | | |
|---|---|---|---|---|
| **Variable** | **Baseline** | **Stage 1** | **Stage 2** | **Stage 3** |
| LVIDd (mm) | 3.7 ± 0.08 | 3.7 ± 0.07 | 3.9 ± 0.10 | 4.2 ± 0.12[b] |
| LVIDs (mm) | 2.4 ± 0.06 | 2.7 ± 0.08 | 3.1 ± 0.10[c] | 3.5 ± 0.09[c] |
| IVSd (mm) | 0.76 ± 0.02 | 0.77 ± 0.02 | 0.7 ± 0.02[a] | 0.68 ± 0.02[a] |
| IVSs (mm) | 1.17 ± 0.04 | 1.11 ± 0.03 | 0.89 ± 0.03[c] | 0.81 ± 0.03[c] |
| LVFWd (mm) | 0.77 ± 0.02 | 0.77 ± 0.02 | 0.72 ± 0.02 | 0.71 ± 0.01 |
| LVFWs (mm) | 1.14 ± 0.04 | 1.17 ± 0.03 | 1.09 ± 0.03 | 0.99 ± 0.01[b] |
| EDVI (ml/m$^2$) | 31.7 ± 2.8 | 41.3 ± 3.0 | 60.7 ± 4.5[c] | 80.0 ± 4.1[c] |
| ESVI (ml/m$^2$) | 91.5 ± 5.0 | 93.6 ± 4.6 | 107.8 ± 6.1 | 127.7 ± 7.4[b] |
| %IVS (%) | 55 ± 7.1 | 45 ± 2.8 | 26 ± 3.3[c] | 20 ± 4.7[c] |
| %LVFW (%) | 49 ± 6.2 | 51 ± 3.7 | 52 ± 4.4 | 39 ± 4.6 |
| EF (%) | 65 ± 1.8 | 56 ± 1.8[b] | 44 ± 1.5[c] | 37 ± 2.2[c] |
| HR (beats/min) | 110 ± 8.2 | 123 ± 5.3 | 111 ± 6.4 | 130 ± 11.6 |
| SIteichholz (ml/beat • m$^2$) | 60 ± 3 | 52 ± 2 | 47 ± 2[b] | 48 ± 5[a] |
| CIteichholz (L/m2 • min) | 6.6 ± 0.5 | 6.5 ± 0.4 | 5.3 ± 0.5 | 6.4 ± 0.9 |
| PFVaortic (m/s) | 1.4 ± 0.08 | 1.1 ± 0.04[b] | 0.9 ± 0.04[c] | 0.9 ± 0.04[c] |
| ATaortic (msec) | 57 ± 3.5 | 67 ± 2.3[a] | 73 ± 2.3[c] | 69 ± 2.4[b] |
| SIdoppler (ml/beat • m$^2$) | 43 ± 3 | 34 ± 2[a] | 29 ± 2[c] | 28 ± 1[c] |
| CIdoppler (L/min • m$^2$) | 4.6 ± 0.2 | 4.3 ± 0.3 | 3.3 ± 0.3[a] | 3.7 ± 0.4 |
| PFVpulmonary (m/s) | 0.9 ± 0.04 | 0.7 ± 0.03[c] | 0.6 ± 0.03[c] | 0.6 ± 0.04[c] |
| ATpulmonary (msec) | 99 ± 4.1 | 106 ± 9.5 | 115 ± 4.3 | 115 ± 4.9 |

LVIDd = Left ventricular internal diameter at end diastole. LVIDs = Left ventricular internal diameter at end systole. IVSd = Interventricular septal thickness at end diastole. IVSs = Interventricular septal thickness at end systole. LVFWd = Left ventricular free wall thickness at end diastole. LVFWs = Left ventricular free wall thickness at end systole. EDVI = End-diastolic left ventricular volume index. ESVI = End-systolic left ventricular volume index. %IVS = Fractional thickening of the interventricular septum. %LVFW = Fractional thickening of the left ventricular free wall. EF = Ejection fraction. HR = Heart rate. SIteicholz = Stroke index calculated by use of the Teichholz formula. CIteicholz = Cardiac index calculated by use of the Teichholz formula. PFVaortic = Peak flow velocity at the aortic valve. ATaortic = Acceleration time at the aortic valve. SIdoppler = Stroke index calculated by use of Doppler indices. CIdoppler = Cardiac index calculated by use of Doppler indices. PFVpulmonary = Peak flow velocity at the pulmonary valve. ATpulmonary = Acceleration time at the at the pulmonary valve.

[a]Significantly ($P < 0.05$) different from baseline value. [b]Significantly ($P < 0.01$) different from baseline value. [c]Significantly ($P < 0.001$) different from baseline value.

Table 2—Effects of dobutamine infusion on echocardiographic indices of systolic function in 7 male Beagles before (baseline) and after development of pacing-induced ELVD

| Variable | Baseline | ELVD | | |
|---|---|---|---|---|
| | | Stage 1 | Stage 2 | Stage 3 |
| FS (%) | | | | |
| 0 mg/kg/min* | 35 ± 1.3 | 29 ± 1.3[a] | 22 ± 0.9[a] | 18 ± 1.2[a] |
| 12.5 mg/kg/min | 44 ± 1.3[b] | 37 ± 1.1[b] | 28 ± 0.8[b] | 24 ± 1.3[b] |
| 22.5 mg/kg/min | 51 ± 2.4[b] | 41 ± 1.2[b] | 33 ± 1.1[b] | 28 ± 1.3[b] |
| 32.5 mg/kg/min | 55 ± 2.2[b] | 46 ± 1.6[b] | 38 ± 1.6[b] | 31 ± 0.9[b] |
| 42.5 mg/kg/min | 59 ± 2.3[b] | 51 ± 1.2[b] | 39 ± 1.0 | 34 ± 1.4 |
| MPC† | 67 ± 9.0 | 79 ± 6.8 | 84 ± 6.3 | 99 ± 15.6 |
| PEP (msec) | | | | |
| 0 mg/kg/min* | 57 ± 2.2 | 80 ± 2.2[a] | 87 ± 4.1[a] | 81 ± 3.2[a] |
| 12.5 mg/kg/min | 46 ± 2.4[b] | 56 ± 2.3[b] | 65 ± 2.6[b] | 61 ± 2.8[b] |
| 22.5 mg/kg/min | 36 ± 2.3[b] | 46 ± 1.6[b] | 51 ± 1.3[b] | 56 ± 1.4[b] |
| 32.5 mg/kg/min | 34 ± 1.7 | 41 ± 1.8[b] | 47 ± 1.4[b] | 49 ± 1.4[b] |
| 42.5 mg/kg/min | 28 ± 2.1[b] | 38 ± 1.8[b] | 43 ± 1.4[b] | 47 ± 1.5 |
| MPC† | −50 ± 2.6 | −53 ± 2.3 | −50 ± 1.7 | −41 ± 3.3[a] |
| LVET (msec) | | | | |
| 0 mg/kg/min* | 169 ± 7 | 153 ± 2[a] | 152 ± 3[a] | 148 ± 5[a] |
| 12.5 mg/kg/min | 157 ± 5[b] | 150 ± 4 | 154 ± 3 | 149 ± 4 |
| 22.5 mg/kg/min | 142 ± 3[b] | 136 ± 5[b] | 146 ± 3[b] | 144 ± 5 |
| 32.5 mg/kg/min | 123 ± 2[b] | 123 ± 4[b] | 140 ± 3[b] | 140 ± 5 |
| 42.5 mg/kg/min | 104 ± 3[b] | 118 ± 4 | 130 ± 3[b] | 134 ± 5 |
| MPC† | −38 ± 3.2 | −22 ± 2.6[a] | −14 ± 1.4[a] | −9 ± 2.4[a] |
| PEP/LVET | | | | |
| 0 mg/kg/min* | 0.34 ± 0.02 | 0.52 ± 0.02[a] | 0.57 ± 0.02[a] | 0.55 ± 0.03[a] |
| 12.5 mg/kg/min | 0.29 ± 0.01 | 0.37 ± 0.02[b] | 0.42 ± 0.02[b] | 0.41 ± 0.02[b] |
| 22.5 mg/kg/min | 0.25 ± 0.02 | 0.34 ± 0.02[b] | 0.35 ± 0.01[b] | 0.39 ± 0.02 |
| 32.5 mg/kg/min | 0.27 ± 0.01 | 0.34 ± 0.02 | 0.33 ± 0.02 | 0.35 ± 0.02[b] |
| 42.5 mg/kg/min | 0.27 ± 0.02 | 0.32 ± 0.02 | 0.33 ± 0.01 | 0.35 ± 0.01 |
| MPC† | −19 ± 7.1 | −38 ± 2.9[a] | −42 ± 1.9[a] | −36 ± 2.5[a] |
| mVcf (circ/s) | | | | |
| 0 mg/kg/min* | 2.1 ± 0.19 | 1.9 ± 0.12 | 1.4 ± 0.06[a] | 1.2 ± 0.10[a] |
| 12.5 mg/kg/min | 2.8 ± 0.2[b] | 2.5 ± 0.13[b] | 1.8 ± 0.07[b] | 1.7 ± 0.11[b] |
| 22.5 mg/kg/min | 3.6 ± 0.15[b] | 3.1 ± 0.19[b] | 2.3 ± 0.10[b] | 2.0 ± 0.13[b] |
| 32.5 mg/kg/min | 4.4 ± 0.23[b] | 3.8 ± 0.28[b] | 2.8 ± 0.13[b] | 2.2 ± 0.12[b] |
| 42.5 mg/kg/min | 5.6 ± 0.13[b] | 4.4 ± 0.24[b] | 3.1 ± 0.12[b] | 2.5 ± 0.12 |
| MPC† | 174 ± 24 | 136 ± 13 | 115 ± 8[a] | 118 ± 16[a] |

Values reported as mean ± SEM.
*Dobutamine dosage. †MPC = [(value at 42.5 mg/kg/min − value at 0 mg/kg/min)/value at 0 mg/kg/min] × 100.
FS = Fractional shortening of the left ventricle. MPC = Maximal percentage change. PEP = Pre-ejection period of the left ventricle. LVET = Left ventricular ejection time. mVcf = Mean velocity of fiber shortening.
[a]Significantly ($P < 0.05$) different from baseline value. [b]Significantly ($P < 0.05$) different from previous dobutamine dosage.

## Results

**Effects of RRVP on predobutamine measurements**—Before activation of the pacemakers on day 0, all dogs were clinically normal. Mean (± SEM) body weight was 16.3 ± 0.8 kg, rectal temperature was 38.9 ± 0.5 C, respiratory rate was 32 ± 4 breaths/min, and heart rate was 110 ± 8 beats/min. During the pacing period, significant changes in these variables were not detected. However, the femoral pulse became weak in all dogs, and a moderate systolic murmur indicative of mitral valve regurgitation was audible in 1 dog at stage 3. After activation of the pacemaker, 1 of the 3 stages of ELVD was diagnosed in all dogs at each examination. Stage 1 was diagnosed in a mean of 6 ± 0.8 days, stage 2 in 13 ± 1.1 days, and stage 3 in 19 ± 1.3 days.

Electrocardiographic evidence of atrial or ventricular enlargement was not detected either on day 0 or at any time during the pacing period. However, monomorphic isolated left ventricular premature beats (mean frequency, 10 beats/min) were observed in 1 dog with stage-3 ELVD. Radiography revealed that stage of ELVD did not have a significant ($P = 0.78$) effect on the sum of the long and short axes of the heart. A slight pulmonary interstitial pattern was seen on thoracic radiographs obtained from 1 dog with stage-3 ELVD.

A significant ($P < 0.001$) decrease in SABP was detected during development of ELVD. Mean SABP on day 0 was163 ± 6 mm Hg, whereas SABP was 150 ± 4, 120 ± 9, and 121 ± 13 mm Hg at stages 1, 2, and 3 of ELVD, respectively.

Rapid right ventricular pacing induced a significant increase in predobutamine values for LVIDd, LVIDs, EDVI, ESVI, PEP, and PEP/LVET (**Tables 1 and 2**). Diastolic interventricular septum thickness, IVSs, LVFWs, %FS, %IVS, LVET, mVcf, and %EF decreased significantly during the pacing period, whereas LVFWd and %LVFW were unchanged.

Peak flow velocity, **DT at the aortic valve (DTaortic)**, and DTpulmonary significantly decreased, whereas **AT at the aortic valve (ATaortic)** significantly increased during the pacing period, compared with baseline values. Therefore, AT/DTpulmonary and the **ratio of**

Table 3—Effects of dobutamine infusion on Doppler indices of systolic left and right cardiac function in 7 male Beagles before (baseline) and after development of pacing-induced ELVD

| Variable | Baseline | ELVD | | |
|---|---|---|---|---|
| | | Stage 1 | Stage 2 | Stage 3 |
| DTaortic (msec) | | | | |
| 0 mg/kg/min* | 121 ± 7 | 101 ± 6[a] | 94 ± 2[a] | 86 ± 2[a] |
| 12.5 mg/kg/min | 112 ± 4 | 105 ± 3 | 102 ± 3[b] | 95 ± 3 |
| 22.5 mg/kg/min | 102 ± 2[b] | 94 ± 3[b] | 98 ± 3 | 89 ± 3 |
| 32.5 mg/kg/min | 77 ± 6[b] | 85 ± 3[b] | 97 ± 3 | 93 ± 3 |
| 42.5 mg/kg/min | 59 ± 7[b] | 71 ± 3[b] | 89 ± 3[b] | 86 ± 3 |
| MPC† | −57 ± 3.7 | −27 ± 4.2[a] | −4 ± 3[a] | 0 ± 4.6[a] |
| AT/DTaortic | | | | |
| 0 mg/kg/min* | 0.5 ± 0.05 | 0.7 ± 0.05[a] | 0.8 ± 0.03[a] | 0.8 ± 0.07[a] |
| 12.5 mg/kg/min | 0.5 ± 0.05 | 0.6 ± 0.02[b] | 0.6 ± 0.04[b] | 0.7 ± 0.05 |
| 22.5 mg/kg/min | 0.4 ± 0.03 | 0.6 ± 0.04 | 0.6 ± 0.04 | 0.7 ± 0.05 |
| 32.5 mg/kg/min | 0.6 ± 0.05[b] | 0.6 ± 0.04 | 0.6 ± 0.03 | 0.6 ± 0.03 |
| 42.5 mg/kg/min | 0.8 ± 0.05[b] | 0.7 ± 0.04[b] | 0.6 ± 0.03 | 0.6 ± 0.06 |
| MPC† | 83 ± 17 | 4 ± 7.4[a] | −24 ± 4.5[a] | −25 ± 5.4[a] |
| DTpulmonary (msec) | | | | |
| 0 mg/kg/min* | 95 ± 6 | 82 ± 3[a] | 86 ± 4 | 72 ± 3[a] |
| 12.5 mg/kg/min | 79 ± 6[b] | 74 ± 4 | 81 ± 3 | 72 ± 3 |
| 22.5 mg/kg/min | 71 ± 9 | 66 ± 4 | 80 ± 4 | 73 ± 3 |
| 32.5 mg/kg/min | 62 ± 6 | 66 ± 4 | 73 ± 3 | 66 ± 3 |
| 42.5 mg/kg/min | 50 ± 4[b] | 56 ± 3[b] | 71 ± 4[b] | 67 ± 4 |
| MPC† | −46 ± 5 | −31 ± 4 | −15 ± 6[a] | −7 ± 4[a] |
| AT/DTpulmonary | | | | |
| 0 mg/kg/min* | 1.1 ± 0.1 | 1.3 ± 0.1 | 1.4 ± 0.1 | 1.6 ± 0.1[a] |
| 12.5 mg/kg/min | 1.1 ± 0.1 | 1.4 ± 0.1 | 1.2 ± 0.1 | 1.4 ± 0.1 |
| 22.5 mg/kg/min | 1.2 ± 0.1 | 1.4 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1[b] |
| 32.5 mg/kg/min | 1.3 ± 0.2 | 1.2 ± 0.1[b] | 1.1 ± 0.1[b] | 1.3 ± 0.1[b] |
| 42.5 mg/kg/min | 1.4 ± 0.1 | 1.3 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1[b] |
| MPC† | 33 ± 12 | −6 ± 9[a] | −10 ± 9[a] | −25 ± 6[a] |

*See* Table 2 for key.
DTaortic = Deceleration time at the aortic valve. AT/DTaortic = Ratio of ATaortic to DTaortic. DTpulmonary = Deceleration time at the pulmonary valve. AT/DTpulmonary = Ratio of ATpulmonary to DTpulmonary.

**AT to DT at the aortic valve (AT/D Taortic)** increased significantly during the pacing period (**Table 3**). Rapid right ventricular pacing induced a significant decrease in MVE but not MVA, resulting in a significant decrease in mitral E/A during the pacing period, compared with baseline values (**Table 4**).

Rapid right ventricular pacing also induced a significant decrease in SIecho and SIdoppler. However, heart rate was not significantly affected. Cardiac index measured by use of the Doppler technique decreased throughout the pacing period, compared with baseline values, but the decrease was only significant at stage 2 of ELVD.

**Results of dobutamine stress tests—**All dogs tolerated the DST. Ventricular premature beats detected in 1 dog before dobutamine infusion did not increase in frequency during the DST. Two dogs panted during the test, and 1 dog vomited after receiving dobutamine at a dosage of 32.5 µg/kg/min. The test did not have to be interrupted in any dog.

Values for %FS, PEP, LVET, PEP/LVET, and mVcf determined after dobutamine infusion during the pacing period were significantly different from baseline values (Table 2). Maximal percentage change of %FS did not significantly differ among stages, but %FS in dogs at stages 2 and 3 of ELVD reached a steady state at a dobutamine dosage of 32.5 µg/kg/min. The MPC of LVET was significantly less at all stages of ELVD, compared with baseline values, whereas the MPC of PEP was significantly less than the baseline value only at stage 3. Therefore, the dobutamine-induced maximal decrease in PEP/LVET was significantly greater during the pacing period, and the maximal increase in mVcf was significantly less at stages 2 and 3 of ELVD, compared with baseline values.

Values for DTaortic, AT/DTaortic, DTpulmonary, AT/DTpulmonary, MVE, MVA, and mitral E/A determined after dobutamine infusion during the pacing period were significantly different, compared with baseline values (Tables 3 and 4). Dobutamine-induced decreases in DTaortic and DTpulmonary were significantly less during the pacing period, compared with baseline values. Consequently, AT/DTaortic significantly increased during the baseline DST, compared with predobutamine values, whereas this ratio remained constant with predobutamine values at stage 1 of ELVD and significantly decreased at stages 2 and 3. The AT/DTpulmonary was not significantly different after dobutamine infusion on day 0 or at stages 1 and 2 of ELVD, compared with predobuatamine values, but AT/DTpulmonary decreased significantly at stage 3. The dobutamine-induced increase in MVE (ie, MPC of MVE) was significantly greater and the increase in MVA significantly less during the pacing period, compared with baseline values (Table 4). Therefore, in dogs without ELVD, mitral E/A decreased significantly at high dobutamine dosages, whereas at stages 1, 2, and 3 of ELVD, this ratio increased significantly during DST.

Dobutamine infusion resulted in a significant

Table 4—Effects of dobutamine infusion on Doppler indices of mitral flow in 7 male Beagles before (baseline) and after development of pacing-induced ELVD

| Variable | Baseline | ELVD | | |
|---|---|---|---|---|
| | | Stage 1 | Stage 2 | Stage 3 |
| MVE (m/s) | | | | |
| 0 mg/kg/min* | 0.7 ± 0.03 | 0.6 ± 0.03[a] | 0.5 ± 0.03[a] | 0.5 ± 0.04[a] |
| 12.5 mg/kg/min | 0.8 ± 0.03[b] | 0.8 ± 0.02[b] | 0.7 ± 0.04[b] | 0.7 ± 0.04[b] |
| 22.5 mg/kg/min | 0.9 ± 0.05[b] | 0.9 ± 0.04[b] | 0.8 ± 0.03[b] | 0.9 ± 0.04[b] |
| 32.5 mg/kg/min | 1.0 ± 0.05[b] | 0.9 ± 0.02 | 0.8 ±0.03 | 1.0 ± 0.04[b] |
| 42.5 mg/kg/min | 1.0 ± 0.04 | 1.0 ± 0.02[b] | 0.9 ± 0.03[b] | 1.0 ± 0.04 |
| MPC† | 43 ± 4.9 | 75 ± 7.8 | 90 ± 8.9[a] | 124 ± 21.4[a] |
| MVA (m/s) | | | | |
| 0 mg/kg/min* | 0.4 ±0.03 | 0.5 ± 0.02 | 0.4 ± 0.03 | 0.4 ± 0.04 |
| 12.5 mg/kg/min | 0.5 ± 0.02[b] | 0.6 ± 0.02[b] | 0.5 ± 0.03[b] | 0.5 ± 0.04[b] |
| 22.5 mg/kg/min | 0.6 ± 0.03[b] | 0.6 ± 0.03[b] | 0.6 ± 0.03[b] | 0.5 ± 0.04 |
| 32.5 mg/kg/min | 0.8 ± 0.03[b] | 0.6 ± 0.03 | 0.6 ± 0.04 | 0.6 ± 0.04[b] |
| 42.5 mg/kg/min | 0.8 ± 0.06 | 0.7 ± 0.01 | 0.6 ± 0.04 | 0.6 ± 0.04 |
| MPC† | 81 ± 7.2 | 36 ± 8.3[a] | 52 ± 8.4[a] | 56 ± 10.6[a] |
| Mitral E/A | | | | |
| 0 mg/kg/min* | 1.6 ± 0.09 | 1.2 ± 0.05[a] | 1.1 ± 0.09[a] | 1.1 ± 0.01[a] |
| 12.5 mg/kg/min | 1.6 ± 0.10 | 1.3 ± 0.05 | 1.3 ± 0.06[b] | 1.4 ± 0.09[b] |
| 22.5 mg/kg/min | 1.4 ± 0.10 | 1.3 ± 0.05 | 1.4 ± 0.06 | 1.6 ± 0.07[b] |
| 32.5 mg/kg/min | 1.3 ± 0.07[b] | 1.4 ± 0.05 | 1.3 ± 0.06 | 1.6 ± 0.07 |
| 42.5 mg/kg/min | 1.3 ± 0.07 | 1.5 ± 0.03[b] | 1.4 ± 0.06 | 1.6 ± 0.10 |
| MPC† | −19 ± 3.3 | 21 ± 6.1[a] | 26 ± 8.6[a] | 45 ± 13.7[a] |

*See* Table 2 for key.
MVE = Peak velocity of the mitral E wave. MVA = Peak velocity of the mitral A wave. Mitral E/A = Ratio of MVE to MVA.

increase in SABP, CIecho, and CIdoppler before and during the pacing period. However, values obtained during the baseline DST were not significantly different from values obtained during the pacing period. Mean SAPB obtained after infusion of 42.5 µg of dobutamine/kg/min on day 0 was 205 ± 14 mm Hg, CIecho was 11.8 ± 1.2 L/min, and CIdoppler was 7.5 ± 0.4 L/min. The MPC of heart rate was significantly less at stage 3 of ELVD, compared with the baseline value; values were 63 ± 8, 52 ± 6, 47 ± 7, and 31 ± 9% at baseline and stages 1, 2, and 3 of ELVD, respectively. End diastolic volume index was not affected by dobutamine infusion in dogs at baseline or at any time during the pacing period.

## Discussion

Rapid right ventricular pacing is a reliable experimental technique to induce congestive heart failure and is more reproducible and less traumatic than most other techniques.[16] An additional feature of this model is that cardiac failure can be rapidly reversed by discontinuing pacing. Moreover, clinical, radiographic, hemodynamic, and echocardiographic changes observed in animals subjected to RRVP are comparable to those observed in humans or dogs with naturally occurring DCM.[16-18] In dogs, RRVP at a rate of approximately 240 beats/min induces clinical signs of advanced congestive heart failure in 3 to 4 weeks,[16] whereas RRVP at a rate of 180 beats/min for 10 days induces a stage of left ventricular dysfunction that does not result in clinical signs.[19] In the study reported here, the rate and duration of RRVP (180 beats/min for 10 days followed by 215 beats/min for 7 to 15 days) was chosen to induce 3 progressive stages of ELVD that resulted in no or mild clinical signs. Our model was characterized by a progressive alteration of values for most Doppler echocardiographic variables that assess left ventricular systolic function as well as left ventricular dilatation in stage 3. Clinical signs of overt congestive heart failure, such as lethargy, decreased food intake, ascites, and edema, did not develop.[18] Therefore, this model mimics the clinical appearance of dogs with early naturally occurring DCM.

We found that values for most Doppler echocardiographic variables of systolic cardiac function obtained before DST were significantly affected by RRVP. Similar changes in results of resting echocardiography have been described in Doberman Pinschers,[11] Newfoundlands,[6] and Irish Wolfhounds[20] asymptomatic for clinical signs of DCM. The decrease in PFV at the aortic valve and DTaortic and the increase in ATaortic also mimicked alterations detected in humans with naturally occurring DCM.[21]

We also detected a progressive decrease in MVE with no associated change in MVA prior to dobutamine infusion during the pacing period. This resulted in a decrease in mitral E/A. Peak flow velocity of the mitral E wave is essentially dependent on left atrial pressure, left ventricular relaxation rate, and left ventricular end systolic volume.[22-25] We found ESVI progressively increased prior to DST as the stage of ELVD increased. We did not measure left atrial pressure and left ventricular relaxation rate. A decrease in mitral E/A has been reported in humans with DCM but without mitral regurgitation with a prolonged relaxation time and left ventricular filling pressure within reference range.[26] Moreover, in dogs with progressive heart failure induced by intracoronary embolization, a progressive decrease in MVE has been detected.[25] In Doberman Pinschers with occult DCM, resting mitral E/A was not significantly reduced.[11] Because RRVP induces changes in the relaxation rate of the left ventricle,[27,28] the decrease in MVE that we detected may be attributable to a decrease in relaxation rate of the left ventricle associated with an increase in ESVI before development of a severe increase in preload.

However, a more complete evaluation of diastolic function is needed to confirm this hypothesis.

In the present study, SI significantly decreased during the pacing period, compared with prepacing values. Cardiac index decreased, and heart rate increased during the pacing period, but these changes were not significant. The small number of dogs that we used in this study probably limited our ability to detect significant differences in these variables. Three compensatory mechanisms can be initiated to maintain cardiac output, including an increase in heart rate, decrease in afterload, and increase in preload. Preload, estimated by EDVI, significantly increased during development of ELVD; we did not specifically assess afterload. However, the significant decrease in SABP as a result of RRVP led us to suspect a decrease in afterload.

Prior to the pacing period, dobutamine infusion led to an increase in CI; this increase was maintained in dogs with ELVD. This result is in accordance with results obtained from studies of long-term human survivors of childhood cancer asymptomatic for myocardial dysfunction.[29] In contrast, in dogs with clinical signs of heart failure induced by RRVP[27] and in humans with class III or IV heart failure, dobutamine infusion significantly affected CI.[30,31]

Left ventricular ejection time decreased to a lesser degree during dobutamine infusion in dogs after pacing, compared with prepacing values. Systolic time intervals reflect global left ventricular systolic function. Left ventricular ejection time is dependent on myocardial contractility, preload, afterload, and heart rate.[32] In our study, the relative increase in SABP, an estimate of afterload, induced by dobutamine infusion was similar in dogs before and after RRVP, whereas EDVI, an estimate of preload, remained constant, and the MPC of heart rate was significantly decreased at stage 3 of ELVD, compared with the baseline value. Therefore, the change in LVET in response to dobutamine infusion in dogs after development of ELVD was related to a smaller increase in contractility and heart rate. Consequently, dobutamine infusion induced a smaller increase in mVcf and a larger decrease in PEP/LVET after RRVP, compared with prepacing values. The decrease in PEP/LVET observed in dogs with ELVD during infusion of high dosages of dobutamine resulted in values similar to those for healthy dogs. This result was also observed in Doberman Pinschers with early DCM subjected to a weak inotropic challenge.[11]

The significant decrease in mitral E/A that we detected during the baseline DST was in accordance with results obtained with healthy humans subjected to a high-dose DST.[33] Comparable results were also reported from a study of healthy humans subjected to an exercise stress test.[34] On the other hand, in healthy humans[35] and healthy Doberman Pinschers,[11] low-dose dobutamine infusion resulted in an increase in MVE with no change in mitral E/A. These differences could be explained by the dose-dependent importance of the lusitropic, inotropic, and chronotropic effects of dobutamine, as well as by the position of the sample volume in each study.

Although dobutamine infusion resulted in a decrease in mitral E/A prior to development of ELVD, mitral E/A increased during dobutamine infusion at all stages of ELVD. This increase was associated with a more pronounced increase in MVE and a less pronounced increase in MVA during the pacing period, compared with prepacing values. Peak velocity of the mitral E wave is primarily dependent on left atrial pressure, left ventricular relaxation rate, and left ventricular end-systolic volume.[22-25] In our study, dobutamine infusion induced a comparable decrease in ESVI at all stages of ELVD. Moreover, left atrial pressure has been shown to remain constant during dobutamine infusion in healthy dogs and dogs with clinical signs of cardiac failure induced by RRVP.[27,28] The lusitropic activity of dobutamine has also been shown to be preserved in these dogs.[27,28] Therefore, the more pronounced increase in MVE that we detected during the pacing period, compared with prepacing values, may be attributable to a more pronounced dobutamine-induced improvement of left ventricular relaxation rate in dogs with ELVD. The primary hemodynamic determinants of MVA are heart rate, atrial contractility, and atrial afterload.[22-25] Dobutamine has no effect on left ventricular end diastolic pressure and left ventricular distensibility,[27,28] the 2 determinants of atrial afterload. Moreover, chronotropic competence was maintained in dogs with stage-2 ELVD but was decreased at stage 3. This suggests that the less pronounced increase in MVA that we detected during the pacing period was related to a decrease in the inotropic and chronotropic responses of the left atrium to β-adrenergic stimulation. However, a more complete evaluation of diastolic cardiac function is needed to confirm this hypothesis. Mitral E/A also does not decrease in humans with systolic dysfunction subjected to an exercise stress test.[34]

Cardiac and noncardiac adverse effects associated with high-dose DST have been described in humans.[36] We did not detect cardiac adverse effects in the dogs described in this report, even at high nontherapeutic dosages of dobutamine. However, because we only examined Beagles, the safety of the DST cannot be extrapolated to other breeds predisposed to cardiac arrhythmias or to dogs with naturally occurring DCM. Noncardiac adverse effects described in our study were vomiting and panting. Vomiting observed in 1 dog after infusion of 32.5 μg of dobutamine/kg/min resolved without medical treatment and without stopping dobutamine infusion. However, vomiting temporarily disturbed dobutamine response because of vagal reflex and forced us to prolong dobutamine infusion. From our experience, we believe that administration of dobutamine at progressively higher infusion dosages, instead of at a single high dosage, reduces the development of adverse effects. Panting that developed in 2 dogs during the DST increased the difficulty of echocardiography.

Differences in DST values between the prepacing and pacing period were more pronounced when higher dosages of dobutamine were administered. In humans, results of high-dose DST are a superior diagnostic tool, compared with results of low-dose DST; dobutamine dosages up to 40 or 50 μg/kg/min are usually used.[36] In a similar manner, high-dose DST may provide more accurate assessment of cardiac function

in dogs. In our study, dogs lay quietly on a table for approximately 1 hour and 15 minutes. The duration of this test may be too long for many dogs. Thus, infusion duration for each dobutamine dosage may need to be reduced by measuring only those variables that provide the most accurate assessment of cardiac function. On the basis of our results, we suggest that an M-mode view of the left ventricle at the level of the chordae tendinae, a Doppler recording of aortic flow, and a Doppler recording of mitral flow be obtained during high-dose DST to allow early detection of global cardiac dysfunction similar to that which develops in dogs with DCM.

[a]Thin Line EZ, Model 438-10, Intermedics, Brussels, Belgium.
[b]Dart, Model 292-05, Intermedics, Brussels, Belgium.
[c]Model 811 BTS, Parks Medical Electronics Inc, Aloka, Ore.
[d]RT6800, GE Medical Systems, London, UK.
[e]H4165B, GE Medical Systems, London, UK.
[f]H4168B, GE Medical Systems, London, UK.

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