Dobutamine Stress Echocardiography for Assessment of Systolic Function in Dogs with Experimentally Induced Mitral Regurgitation

R. Suzuki, H. Matsumoto, T. Teshima, Y. Mochizuki, and H. Koyama

**Background:** Systolic dysfunction is associated with poor outcomes in dogs with myxomatous mitral valve disease. However, assessment of systolic variables by conventional echocardiographic methods is difficult in these dogs because of mitral regurgitation (MR).

**Hypothesis:** We hypothesized that assessment of systolic function by dobutamine stress may identify systolic dysfunction in dogs with MR, and that 2-dimensional speckle-tracking echocardiography (2D-STE) could quantitatively evaluate myocardial function.

**Animals:** Anesthetized dogs with experimentally induced MR.

**Methods:** Dogs were examined for systolic myocardial deformations using 2D-STE during dobutamine infusion before and 3 and 6 months after MR induction. We evaluated peak systolic rotation and rotation rate in each basal and apical view; peak systolic torsion and torsion rate were also calculated.

**Results:** Invasive peak positive first derivatives of left ventricular pressure (dp/dt) were significantly decreased in dogs 6 months after induction of MR compared with pre-MR results. After 3 and 6 months of MR, dogs had diminished peak systolic torsion values and torsion rates in response to dobutamine infusion compared with pre-MR results (3 months, $P < .001$ and $P = .006$; 6 months, $P = .003$ and $P = .021$). These results were significantly correlated with overall invasive dp/dt ($r = 0.644$, $P < .001$; $r = 0.696$, $P < .001$).

**Conclusions and Clinical Importance:** Decreased torsion during dobutamine infusion in dogs with MR may reflect latent systolic dysfunction. Dobutamine infusion, therefore, may be useful for the assessment of systolic function in dogs with MR.

**Key words:** Mitral valve disease; Myocardium; Speckle-tracking; Torsion.

**Abbreviations:**
- **2D-STE** 2-dimensional speckle-tracking echocardiography
- **dp/dt** peak positive first derivatives of the left ventricular pressure
- **EDVI** end-diastolic volume index
- **EF** ejection fraction
- **ESVI** end-systolic volume index
- **FS** fractional shortening
- **IVSd** end-diastolic interventricular septum thickness
- **LA/Ao** left atrial-to-aortic root ratio
- **LV** left ventricular
- **LVWd** end-diastolic left ventricular free-wall thickness
- **MMVD** myxomatous mitral valve disease
- **MR** mitral regurgitation
- **PEP/ET** pre-ejection period-to-ejection time ratio
- **RF** regurgitant fraction
- **RWT** relative wall thickness
- **TSVI** total stroke volume index

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infusion. Although assessment of systolic function by conventional echocardiography is often subjective, 2D-STE can quantitate myocardial deformations during dobutamine infusion. We hypothesized that an inotropic challenge with dobutamine, as assessed by 2D-STE, could reveal early occult cardiac dysfunction not evident at rest.

To our knowledge, assessment of systolic function by a dobutamine stress test, with 2D-STE, in dogs with experimentally induced chronic MR has not been reported previously. Therefore, the purpose of this study was to quantitatively measure myocardial deformations during a dobutamine stress test in dogs with experimentally induced chronic MR.

Materials and Methods

Animals

Five healthy male Beagles (body weight, 10.0 ± 1.5 kg; age, 15.6 ± 0.5 months) were used in this study. Before the first assessment, all dogs were judged to be healthy, based on the absence of a history of cardiac signs, as well as normal findings on complete physical examination, CBC, serum biochemistry evaluation, ECG, thoracic radiography, and transthoracic echocardiography. All procedures were performed according to the Guide for Care and Use of Laboratory Animals and approved by the ethical committee for laboratory animal use of Nippon Veterinary and Life Science University, Japan.

Protocol

All dogs were premedicated with butorphanol tartrate (0.2 mg/kg IM), induced by thiopental sodium (25 mg/kg IV), maintained with 1–1.5% isoflurane mixed with 100% oxygen, and manually ventilated. The left or right lateral neck region was clipped, aseptically prepared, and draped. An approximately 5-cm surgical cut-down was performed over the jugular furrow to expose the carotid artery. A microtip catheter with a pressure transducer frequencies, and gain, were kept constant throughout all echocardiographic studies.

Hemodynamic Measurement

Continuous LV pressures and simultaneous ECG data, along with dobutamine stress echocardiography, were obtained before and 3 and 6 months after inducing MR. Peak systolic LV pressure and peak positive first derivatives of LV pressure (dp/dt) were calculated by appropriate software. All hemodynamic data were calculated as mean values from 10 consecutive high-quality pressure measurements.

Dobutamine Stress Echocardiography

We performed dobutamine stress echocardiography on anesthetized dogs before and 3 and 6 months after surgery. Baseline echocardiographic data were obtained, and dobutamine was infused at a dosage of 5 μg/kg/min for 5 minutes and then 10 μg/kg/min for 10 minutes to allow plasma dobutamine concentration to reach a steady state. During infusion of dobutamine, we performed echocardiography measurements including 2D-STE along with previously described hemodynamic measurements. Instrument settings, including pulse and repetition rate, transducer frequencies, and gain, were kept constant throughout all echocardiographic studies.

Standard Echocardiography and 2D-STE

Conventional 2D, M-mode, and Doppler examinations were performed under anesthesia by a single investigator (RS) by an echocardiographic system (Vivid7 dimension) and transducer (7/5S probe), and a simultaneous ECG limb lead II was recorded and displayed on the images. All data were obtained for at least 9 consecutive cardiac cycles in sinus rhythm and at end-expiration. During the procedure, each dog was placed on a table designed to allow echocardiographic examination during cardiac catheterization. The surgical neck region of all dogs was draped and packed with antiseptic dressing, and the dogs were carefully and repeatedly repositioned in right and left lateral recumbency. All hemodynamic and echocardiographic measurements were performed in closed-chest procedures. Images were analyzed by 1 observer using an off-line work station (EchoPac PC, version 108.1.4). The left atrial-to-aortic root ratio (LA/Ao) was obtained from the right parasternal short-axis view by the B-mode method. M-mode measurements were obtained from the right parasternal short-axis view at the level of the chordae tendineae, according to the leading edge-to-leading edge method. These included end-diastolic interventricular septum thickness (IVSd), end-diastolic LV free-wall thickness (LVWd), end-diastolic LV internal dimension (LVIDd), end-systolic LV internal dimension (LVIDs), and fractional shortening (FS). As indicators of LV geometrical remodeling, relative wall thicknesses (RWT) and sphericity indexes were calculated. RWT is the ratio of the sum of IVSd and LVWd to LVIDd, and the sphericity index is the ratio of the LV long axis-to-short axis diameter both in end-systole and in end-diastole. For LV volume measurements, the biplane method of disks (modified Simpson’s rule) was used, based on high-quality left-apical 4- and 2-chamber views, according to the American Society of Echocardiography.
included end-diastolic volume, end-systolic volume, and total stroke volume indexed to body surface area (end-diastolic volume index [EDVI], end-systolic volume index [ESVI], and total stroke volume index [TSVI]). Global ejection fraction (EF) was calculated. Body surface area was derived from each animal’s body weight using a previously published equation.\textsuperscript{17} The LV outflow was obtained from the left-apical 5-chamber view, and pre-ejection period (PEP) and ejection time (ET) were measured; LV PEP/ET was calculated.\textsuperscript{31} Forward SV was also calculated as the product of the aortic valve cross-sectional area (using a circular assumption for the aortic valve annulus) and the aortic valve outflow time-velocity integral\textsuperscript{18} for subsequent calculation of regurgitant fraction (RF) with the formula, RF = [(total stroke volume – forward stroke volume)total stroke volume] × 100. In our analyses, we used the mean of 3 consecutive cardiac cycles in sinus rhythm for each measurement.

After completion of standard echocardiographic examinations, high-quality images for 2D-STE analyses were carefully obtained by the same investigator, using the same protocol. We used previously published procedures for the speckle-tracking analysis.\textsuperscript{4,5,19} For analysis of 2D-STE results, all views were recorded at rates of 76.1–139.2 frames/s. To evaluate torsional deformations, proper basal and apical short-axis views were carefully obtained using the following anatomic landmarks: at the basal level, mitral valve and at the apical level, LV cavity alone with no papillary muscle visible. Images were analyzed by 1 trained observer using an off-line work station.\textsuperscript{1} We obtained peak systolic rotation and rotation rates in each of the apical and basal short-axis planes. Moreover, we calculated peak systolic torsion and torsion rate. The mean values of 3 consecutive cardiac cycles in sinus rhythm were used in all analyses.

### Statistical Analysis

Data are expressed as mean ± SD. All statistical analyses were performed by commercially available computer software.\textsuperscript{8} We used the Shapiro-Wilk test to evaluate the normal distribution of the variables. We used the Tukey HSD test for testing equality of the means at the 3 points (presurgical and after 3 and 6 months of MR) at rest and during dobutamine infusion. To examine correlations between torsional parameters and overall invasive dp/dt, a linear regression analysis was performed. A P value of <.05 was regarded as significant. Intra-observer reproducibility of 2D-STE measurements was assessed by repeating measurements 3 times for 3 dogs selected at random.

### Results

#### Hemodynamic and Standard Echocardiography Data

Baseline (without dobutamine infusion) hemodynamic and standard echocardiography data, before and 3 and 6 months after MR induction, are summarized in Table 1. LA/Ao (P < .001), LVIdd (P = .001), LVIdDs (P = .012), EDVI (P < .001), ESVI (P = .033), TSVI (P = .035), and RF (P < .001) were significantly increased 3 months after induction of MR compared with pre-MR measurements. Three months after induction of MR, the dogs had significantly decreased diastolic and systolic sphericity indexes, and RWT compared with presurgical data (P = .001, P < .001, and P = .045, respectively). LA/Ao (P < .001), LVIdd (P < .001), LVIdDs (P = .006), EDVI (P < .001), ESVI (P = .008), TSVI (P = .002), and RF (P < .001) were significantly increased after

| Pre | 3 Months | 6 Months |
|-----|----------|----------|
| Heart rate (bpm) | 91.1 ± 26.3 | 127.3 ± 48.6 | 102.2 ± 27.5 |
| Peak systolic LV pressure (mmHg) | 102.2 ± 20.6 | 92.4 ± 21.5 | 80.6 ± 8.0 |
| Invasive dp/dt (mmHg/s) | 2.10 | 2.07 ± 377.4 | 630 ± 552.9 | 331.4 ± 156.5 |
| LA/Ao | 1.2 ± 0.1 | 2.0 ± 0.2 | 2.2 ± 0.2 |
| LVIdd (mm) | 26.3 ± 2.5 | 38.7 ± 4.9 | 41.8 ± 2.8 |
| EDVI (mL/m²) | 47.6 ± 11.1 | 90.0 ± 9.1 | 117.9 ± 11.0 |
| TSVI (mL/m²) | 60.5 ± 12.2 | 113.8 ± 42.9 | 153.0 ± 20.8 |
| RF (%) | N.A. | 43.7 ± 20.9 | 56.8 ± 10.1 |

Data are expressed as mean ± SD.

LV, left ventricular; dp/dt, peak positive first derivatives of the left ventricular pressure; LA/Ao, left atrial-to-aortic root ratio; LVIdd, end-diastolic left ventricular internal dimension; EDVI, end-diastolic volume index; TSVI, total stroke volume index; RF, regurgitant fraction; N.A., Not applied.

\textsuperscript{a}Within a row, values differed significantly from pre values.

6 months of induced MR compared with presurgical data. Dogs with a 6-month history of induced MR also had significantly decreased invasive dp/dt (P = .022), diastolic (P < .001) and systolic (P < .001) sphericity indexes, and RWT (P = .022) compared with presurgical data. The systolic sphericity index was also decreased after 6 months compared with after 3 months of induced MR (P = .044). In contrast, heart rate, FS, EF, and PEP/ET were not significantly different at any stage of MR in this study. Selective echocardiography data for baseline (without dobutamine infusion) and dobutamine infusion (10 μg/kg/min) at each time point relative to MR induction are summarized in Table 2. Dogs at 3 and 6 months after MR induction had decreased diastolic sphericity (P < .001 and P < .001) and systolic sphericity (P = .016 and P = .005) in response to dobutamine infusion compared with presurgical dobutamine data. Three months after induction of MR, the dogs had significantly decreased RWT in response to dobutamine infusion compared with presurgical data (P = .03).

#### 2D-STE

Dobutamine stress tests were feasible in the anesthetized dogs at any stage of induced MR in this study. All myocardial segments for speckle-tracking images were analyzed and included in the statistical analyses. The mean of the standard deviation and coefficient of variation were 6.9\% and 6.4\% for peak systolic torsion, and 9.1\%/s and 11.2\% for peak systolic torsion rate.
Table 2. Standard echocardiography data for baseline (without dobutamine infusion) and dobutamine infusion (10 μg/kg/min) before and 3 and 6 months after induction of mitral regurgitation.

|                | Pre       | 3 Months  | 6 Months |
|----------------|-----------|-----------|----------|
| LVIDs (mm)     |           |           |          |
| Baseline       | 19.7 ± 3.6| 27.0 ± 3.9| 28.3 ± 1.2|
| Dobutamine     | 14.3 ± 2.3| 22.0 ± 6.6| 21.8 ± 0.9|
| FS (%)         |           |           |          |
| Baseline       | 25.1 ± 11.8| 29.9 ± 8.6| 32.2 ± 2.6|
| Dobutamine     | 49.9 ± 11.1| 43.3 ± 18.5| 42.9 ± 8.6|
| LV PEP/ET      |           |           |          |
| Baseline       | 0.24 ± 0.07| 0.29 ± 0.05| 0.28 ± 0.07|
| Dobutamine     | 0.15 ± 0.03| 0.20 ± 0.05| 0.23 ± 0.10|
| ESVI (mL/m²)   |           |           |          |
| Baseline       | 59.5 ± 6.1| 57.3 ± 16.4| 62.3 ± 2.7|
| Dobutamine     | 62.0 ± 11.1| 62.5 ± 14.5| 69.3 ± 6.1|
| LVIDs, end-systolic left ventricular internal dimension; FS, fractional shortening; LV PEP/ET, left ventricular pre-ejection period-to-ejection time ratio; EF, ejection fraction; ESVI, end-systolic volume index; RWT, Relative wall thickness. | | | |

Data are expressed as mean ± SD. LVIDs, end-systolic left ventricular internal dimension; FS, fractional shortening; LV PEP/ET, left ventricular pre-ejection period-to-ejection time ratio; EF, ejection fraction; ESVI, end-systolic volume index; RWT, Relative wall thickness.

Discussion

Our findings confirmed that myocardial deformations during dobutamine stress testing could be assessed quantitatively using 2D-STE in dogs with MR. We also confirmed that 2D-STE–derived torsional motions, during dobutamine stress tests, were diminished in anesthetized dogs with severe MR compared with the pre-MR (control) state. Furthermore, these torsional motions were significantly correlated with the overall invasive dp/dt.

Systolic function has been suggested to decrease in dogs with naturally acquired MMVD and in dogs with experimentally induced MR. However, identification of systolic dysfunction is challenging in dogs with MMVD; EF, FS, and PEP/ET at rest and dobutamine infusion could not detect systolic dysfunction. In addition to being dependent on intrinsic contractility, these parameters are also known to be influenced by hemodynamic load and sympathetic tone, which may mask significant myocardial dysfunction in dogs with MR. In contrast, the sphericity index, in both systole and diastole, and RWT were observed to be significantly decreased during disease progression at rest and after dobutamine infusion, findings that agree with previous studies. These geometrical variables may be useful in dogs with MR as part of disease stratification.

Twisting of the left ventricle is determined by the oblique orientation of the myocardial fibers, such that...
2D-STE–derived torsional parameters are more sensitive than conventional echocardiographic parameters for detecting subtle myocardial functional abnormalities. Previous studies have demonstrated that systolic torsion is decreased in animal models of chronic MR, compared with the acute phase in the same individuals. Furthermore, we recently reported that systolic torsion was lower in dogs with advanced MMVD compared with weight- and age-matched healthy controls. The decrease in torsional deformations at baseline (without dobutamine infusion), which agree with previous studies, may reflect deterioration in myocardial contractility with disease progression, although these changes did not reach statistical significance. Small sample size, anesthesia effect, and myocardial compensation remodeling that differ from naturally acquired MMVD may have affected the results of this study.

Given that increased LVIDs and ESVI, and decreased invasive dp/dt, are associated with disease progression, systolic function was decreased in the MR model in this study. During dobutamine infusion, peak systolic torsion and torsional rates were decreased after 3 and 6 months of induced MR in the dogs compared with the presurgical (control) state. Such small responses during dobutamine infusion are believed to reflect systolic dysfunction in dogs with MR. In humans with severe MR, systolic function, as assessed by exercise echocardiography, predicts preservation of LV function and good clinical outcome after medical treatment. Decreased systolic function may also contribute to limitations in exercise capacity in these patients more than the finding of large regurgitant volumes. Although we could not assess exercise capacities and clinical outcomes in this study and the results of this study were not clearly superior to results of resting echocardiography, dobutamine infusion–assessed systolic function in dogs with MR may be an additional tool for detection of the systolic dysfunction. Furthermore, small responses during stress echocardiography might be useful before mitral valve surgery to identify those patients at risk of developing postoperative LV dysfunction.

Dobutamine is a known agonist of the beta-adrenergic receptor, and inability to respond to beta-adrenergic stimulation is a hallmark of the failing human heart. Isolated muscles and myocytes from failing human hearts show decreased inotropic response to beta-adrenergic agonists and down-regulation of beta-adrenergic receptors. Although we could not obtain histopathologic data and the dogs included in this study did not have obvious evidence of heart failure, the responsiveness of dobutamine stress to MR disease progression may suggest the presence of these functional abnormalities.

Left ventricular torsion is also thought to be a mechanism by which the ventricle equalizes transmural oxygen demand gradients, thus minimizing oxygen consumption and optimizing myocardial energetics and efficiency. Increased myocardial oxygen consumption during the dobutamine stress test and decreased oxygen supply because of reduction in forward stroke volume in dogs with severe MR may also contribute to decreased myocardial responsiveness. Therefore, response to dobutamine infusion in dogs with MR may provide additional information for the assessment of progression of disease, treatment responses, and prognosis.

Our study has several limitations. Because of the study design, the effects of anesthesia on myocardial function could not be eliminated. Therefore, our findings should not necessarily be extrapolated to conscious dogs. In this study, MMVD was modeled using young Beagle dogs with a history of up to 6 months of induced MR. However, dogs with naturally occurring, chronic MMVD might have different types of myocardial damage and myocardial function. Although previous studies in dogs demonstrated that dobutamine stress echocardiography was feasible, safe, and repeatable for conscious dogs, older and diseased dogs may experience some adverse effects, such as arrhythmias. Future studies to assess safety in older conscious dogs are needed. Nevertheless, our low-dose protocol, instead of a high-dose dobutamine stress protocol as used in other previous studies, might decrease the development of adverse effects. Calculations of LV torsion depend on the nonsimultaneous measurements of 2 segments (base and apex), which may have affected our results. In addition, myocardial rotation has been
reported to be dependent on transducer angulation and acquiring the true apex of the left ventricle needed for 2D-STE analysis might not be technically feasible. Speckle-imaging, as determined by 3-dimensional echocardiography in a future study, may help to resolve these limitations. Finally, future work incorporating pressure-volume loop analyses for more accurate evaluation of cardiac function is warranted.

In conclusion, indices of geometrical variables at rest (sphericity index and RWT) and during a dobutamine stress test (2D-STE–derived torsional deformations) were decreased with the progression of MR severity. The 2D-STE method can quantitate myocardial deformations during dobutamine infusion, and decreased torsion during dobutamine infusion in dogs with MR may reflect latent systolic dysfunction. Nevertheless, the clinical importance of these findings and their relationship with survival time should be investigated further.

Footnotes

* Vetphale; Meiji Seika, Tokyo, Japan
* Ravonal; Tanabe Mitsubshi Pharma, Osaka, Japan
* Isoflu; Dainippon Sumitomo Pharma, Osaka, Japan
* Model SPR-350, 5Fr; Millar Instruments, Houston, TX
* Marcain 0.5%; AstaZeneca, Osaka, Japan
* Larxin; Taisho Toyama Pharma, Tokyo, Japan
* Methacam 0.15%; Nippon Boehringer Ingelheim, Tokyo, Japan
* SBP2000; Softron, Tokyo, Japan
* Dobutrex; Shionogi & Co, Osaka, Japan
* GE Healthcare, Tokyo, Japan
* SPSS version 15.0J for Windows; SPSS, Tokyo, Japan

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

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