大韓獸醫學會誌(2004) 第44卷 第2號
Korea J Vet Res(2004) 44(2) : 317~322

Quantitative Doppler echocardiography during Dobutamine stress test in canine mitral regurgitant model

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(Accepted: May 10, 2004)

Abstract : This study was performed to evaluate echocardiographic parameters in dogs with experimental mitral regurgitation subjected to dobutamine stress testing. In 8 beagle dogs, a 4-prong grasping forceps was inserted into the left ventricle through the carotid artery with fluoroscopic guidance. The disruption of chordae or mitral valve leaflet was performed. Echocardiographic protocols included quantitative Doppler echocardiography and M-mode measurement for evaluating left ventricle function. After all measurement was obtained at rest, dobutamine was infused incrementally. In stress testing, all measurement also was performed at rest as the same method. In stress Doppler echocardiography, regurgitant fraction and aortic stroke volume was increased significantly ($P<0.001$). Effective regurgitant orifice and regurgitant volume was not changed. In M-mode examination, fractional shortening was increased significantly at stress test ($P<0.001$). From the results obtained in this study, it could be suggested that dobutamine stress echocardiography increase left ventricle performance in non-functional mitral regurgitation and quantitative Doppler echocardiography is non-invasive, accurate method in valvular regurgitation.

Key words : echocardiography, Doppler, Dobutamine, mitral regurgitation, dog

Introduction

Chronic mitral valve insufficiency is the most common heart disease in dogs and is estimated to account for 75 to 80 per cent of cardiac diseases [11]. The severity of regurgitation and effect on ventricular function vary with loading. Symptoms usually appear late, often preceded by latent left ventricular dysfunction that is difficult to detect by measuring conventional ejection indices such as ejection fraction. Therefore, an investigative method of assessing cardiac functional reserve in these dogs may prove useful in establishing a diagnosis prior to development of overt echocardiographic abnormalities.

Doppler echocardiography is a known noninvasive technique of cardiac investigation that offers clinicians a unique opportunity to assess cardiac hemodynamics without risk and discomfort to patients. It also provides a sensitive and simple means of evaluating cardiovascular effects of drugs and procedures [21].

Exercise echocardiography has a role in the evaluation and management of chronic mitral regurgitation. It can assist in the evaluation of symptoms, allow one more fully to assess the mechanism and severity of regurgitation, determine functional capacity, and is increasingly being applied to assess contractile reserve and help optimize the timing of surgical intervention [1].

Dobutamine is a synthetic cathecolamine with relative β1 selectivity. Its major advantages are a great inotropic capability with low chronotropic and arrhythmogenic properties. Moreover, its effects on arterial pressure are minimal [24]. In dogs, conventional therapeutic dosing rates vary from 2.5 to 20 μg/kg/min [17], but in humans, infusion rates up to 50 μg/kg/min are used as a diagnostic tool [26]. Infusion of dobutamine is an alternative to exercise as a means of inducing cardiovascular stress in patients with known or suspected cardiac disease [6, 9, 12]. When associated with noninvasive techniques of cardiovascular investigation (electrocardiography, echocardiography, and noninvasive test blood pressure

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measurement), this pharmacologic test has many advantages. Mainly, it is a noninvasive test of cardiac function. Moreover, high-quality echocardiographic images are more easily obtained during pharmacologic-induced stress than during exercise-induced stress because of the lack of motion and limited interference from respiration. In addition, the amount of stress achieved can easily be controlled and full cooperation of the patient is not required [19]. In veterinary field, study of physiologic response basic echocardiographic indices during dobutamine infusion in healthy dog already reported [13]. However, Doppler echocardiographic indices during dobutamine infusion with experimentally inducing cardiac problem such as mitral regurgitation or myocardial infarction were not reported. Therefore, the purpose of this study was to evaluate echocardiographic parameters including regurgitant fraction and effective regurgitant orifice in dogs with experimental mitral regurgitation subjected to dobutamine stress testing.

Materials and Methods

Experimental canine mitral regurgitation model

Eight adult Beagle dogs (seven male dogs and one female) weighing from 7.7 to 11 kg were selected for investigation. All dogs are fulfilled the following inclusion criteria : no arrhythmia or ischemic heart disease, heart rate in the normal range, no pulmonary disease, no hepatic disease, hematocrit values within the normal range. Eight dogs were anesthetized with isoflurane (Isoflurane®, Rhodia, Bisto, UK) and a 5 Fr. Swan-Ganz catheter (Cook, Bloomington, USA) was passed into the pulmonary artery via the external jugular vein. The measurement of pulmonary capillary wedge pressure and cardiac output were performed with the anesthetic patient monitoring system. Mitral regurgitation was created by cutting the mitral valvular chordae tendinae twice using a 5-Fr, 120-cm long, 4-prong grasping forceps (ESS, New York, USA) inserted into the left ventricle through the carotid artery with fluoroscopic guidance. The disruption of chordae or mitral valve leaflet was performed until there was 100% increase in pulmonary capillary wedge pressure, a grade II/VI or greater left apical holosystolic murmur.

Instruments

Echocardiographic studies were performed using an ultrasound system (Logiq™ 400, GE medical system, Milwaukee, USA) with a multi frequency sector probe. Two dimensional images were obtained using a 6 MHz and Doppler measurement were obtained using a 4 MHz. Selected data were recorded on thermal printing paper (UPP-110HD, SONY Corporation, Tokyo, Japan) and VHS video tape.

Dobutamine stress test

Dobutamine stress test was performed after measuring baseline values. Dobutamine (Dobutamine HCl®, Myung-moon, Hwasung, Korea) was diluted in normal saline to provide a concentration of 500 μg/m*l* which was infused intravenously with syringe pump (Terumo, Tokyo, Japan). Dobutamine infusion was started at 10 μg/kg/min and increasing by 2.5 or 5.0 μg/kg/min every 5-10 minutes to a maximum of 15-30 μg/kg/min. The maximum dose was reached when there was no further increase in cardiac output of when a symptom became intolerable or important arrhythmia developed.

Echocardiographic imaging and analysis

Dogs were conscious during both baseline and dobutamine stress echocardiographic studies. Two dimensional and M-mode images were obtained, using guidelines recommended by the American Society of Echocardiography [20] and the American College of Veterinary Internal Medicine [23]. And volumetric calculations on the basis of the Teicholz formula were used. A long-axis view of left ventricular outflow tract was recorded to measure the diameter of ventricular outflow tract. For Doppler examination, dogs were positioned in left lateral recumbency and two Doppler windows were used to obtain images as parallel as possible to blood flow. The diameter of the mitral annulus (inner edge) and diameter of left ventricle outflow tract (inner edge) were measured at rest and during stress echocardiography with the parasternal long axis view. The mitral annulus stroke volume (MA SV) and left ventricle outflow tract stroke volume (LVOT SV) were calculated as the pulsed-wave Doppler time-velocity integral (TVI) × the area of the annuli of the mitral and aortic valve, respectively [5, 23]. The regurgitant volume (RV) by Doppler was calculated as:

$$\text{RV (Doppler)} = \text{MA SV} - \text{LVOT SV}.$$

The regurgitant fraction (RF) by Doppler was

calculated as:

RF (Doppler) = RV (Doppler) / MA SV.

The maximal regurgitant velocity and the regurgitant time-velocity integral were obtained with continuous wave Doppler echocardiography (Fig. 1). The effective regurgitant orifice (ERO) area was calculated as:

Volume = area × TVI
Area = volume / TVI
ERO = RV / regurgitant TVI.

The stepwise sequence used in all dogs during dobutamine infusion was as follows: LV outflow tract diameter, M-mode examination, LV annulus diameter, mitral inflow time-velocity integral, left ventricle outflow tract time-velocity integral, continuous wave Doppler recording of mitral regurgitation. All records were at least three measurements of each variable.

Statistical analysis

Statistical analysis was performed using the SPSS statistical computer program. Data were analyzed by paired sample *t*-test for paired data comparing base-line values with those obtained after dobutamine infusion. P value < 0.05 was considered significant.

Results

Experimental canine mitral regurgitation model

All of the dogs had mitral regurgitation after inducing and no medication was treated during 1 month. Baseline hemodynamic values indicated mild to moderate mitral regurgitation. Mean regurgitant fractions were 47.0 ± 6.0% at baseline. In M-mode examination, fractional shortenings were 37.8 ± 5.0% within normal range. Stroke volume with Doppler examination was 28.2 ± 3.7 m*l*.

Doppler indices during dobutamine stress test

During dobutamine infusion, mitral annulus inflow was increased from 36.0 ± 5.1 m*l* to 43.8 ± 7.0 m*l* and aortic stroke volume was increased from 18.8 ± 2.4 m*l* to 28.0 ± 3.5 m*l*. The increase was significant (P<0.001). Regurgitant volume and effective regurgitant orifice was not significantly changed. Regurgitant fraction was decreased from 47.0 ± 6.0% to 36.0 ± 6.0% and this decreased was consistent and significant (P < 0.001, Table 1).

M-mode indices during dobutamine stress test

In M-mode examination during dobutamine infusion, end-diastolic volume was not changed significantly. End-systolic volume, stroke volume, ejection fraction

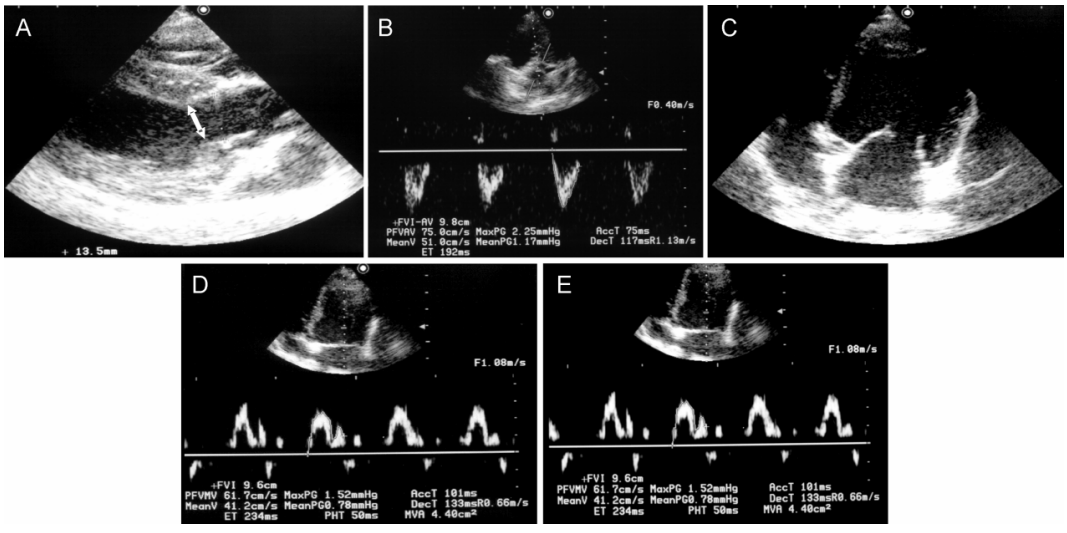

Fig. 1. Quantitative Doppler echocardiographic measurements. A, Measuring left ventricle outflow tract diameter with electrical calipers. B, Tracing left ventricle outflow time-velocity integral (TVI) in pulsed-wave Doppler mode. C, Measuring mitral annulus diameter with electrical calipers. D, Tracing mitral inflow TVI in pulsed-wave Doppler mode. E, Measuring regurgitant flow TVI with continuous wave Doppler mode.

Table 1. Doppler indices at the mitral valves during dobutamine infusion in 8 dogs with mitral regurgitation model

Dog no.	MASV		AOSV		RV		RF		ERO	
	R	D	R	D	R	D	R	D	R	D
1	41.4	49.3	21.8	29.8	19.6	19.5	0.47	0.4	34.6	36.2
2	44.4	48.6	21.0	30.0	23.3	18.6	0.53	0.38	29.3	30.5
3	30.2	33.9	16.4	21.7	13.4	12.2	0.46	0.36	19.4	22.9
4	35.8	43.1	16.3	26.1	19.5	17.0	0.55	0.39	19.9	23.0
5	29.7	35.0	17.7	27.4	11.9	7.6	0.40	0.22	13.3	14.0
6	37.3	54.1	20.9	33.6	16.9	20.5	0.45	0.38	15.8	20.5
7	35.7	45.4	16.4	26.8	19.0	18.7	0.53	0.41	22.3	20.6
8	33.1	40.7	20.1	28.7	13.0	12.0	0.39	0.3	26.5	22.1
Mean	36.0	43.8	18.8	28.0	17.1	15.8	0.47	0.36	22.1	23.7
SD	5.1	7.1	2.4	3.5	4.0	4.6	0.06	0.06	7.4	6.8
P	<0.001		<0.001		NS		<0.001		NS	

HR=heart rate; MASV (AOSV)=mitral annulus (aortic) stroke volume; RV=regurgitant volume; RF=regurgitant fraction; ERO=effective regurgitant orifice; R=rest; D=dobutamine infusion

Table 2. M-mode indices at the left ventricle during dobutamine infusion

Dog no.	EDV		ESV		SV		FS		EF	
	R	D	R	D	R	D	R	D	R	D
1	33.4	31.9	7.4	5.4	26.5	26.4	45.4	49.9	77.88	62.2
2	49.3	44.5	21.8	11.0	27.6	33.6	28.3	42.6	55.67	74.7
3	35.5	37.9	11.1	8.0	24.4	29.9	37.2	46.3	68.8	78.9
4	36.6	42.3	10.7	8.7	25.9	33.6	38.7	46.7	70.54	79.3
5	42.1	47.8	12.5	7.2	29.6	40.4	38.7	53.2	70.35	84.8
6	47.6	63.4	12.7	9.8	34.9	56.6	41.8	52.9	73.46	84.5
7	48.0	36.8	15.8	4.9	32.1	31.9	34.4	55.1	63.23	86.8
8	35.7	49.3	10.8	7.8	24.8	36.4	37.9	50.0	69.6	79.5
Mean	41.0	44.3	12.9	7.9	28.2	36.1	37.8	49.6	68.7	78.8
SD	6.5	9.7	4.3	2.1	3.7	9.3	5.03	4.2	6.7	7.8
P	NS		<0.05		<0.05		<0.001		<0.05	

EDV (ESV)=early diastolic (systolic) volume; SV=stroke volume; FS=fractional shortening; EF=ejection fraction

was significantly changed (P<0.05). Fractional shortening was increased from 37.8±5.0% to 49.6±4.2%. This increase was consistent and significant (P<0.001, Table 2).

Discussion

Doppler echocardiography is a reliable noninvasive method of cardiovascular investigation that can be applied in situations when invasive techniques are unavailable or inappropriate. Doppler echocardiography recently has been developed for use in dogs [10], reference values for several canine Doppler indices have been determined at rest [27]. The problem is overestimation of mitral regurgitation severity in measuring volume accurately [4]. This may be due to an overestimation mitral annular area or an overestimated time-velocity integral (TVI), or both. Sample volume was carefully positioned at the mitral annulus to avoid recording the higher velocities known to be present at the tip of the leaflets [7]. The asymmetrical shape of the mitral annulus is an unlikely explanation of the overestimation because in mitral regurgitation the annulus becomes more circular, and autopsy and four-chamber measurement of mitral annulus are very close [8].

Dobutamine stress echocardiography used as test for the diagnosis of coronary artery disease in patients

unable to exercise in human [18]. The indications of dobutamine echocardiography have expanded into risk stratification of patients undergoing vascular surgery [3], patients with stable chronic coronary disease [16] or previous myocardial infarction, as well as the assessment of myocardial viability [22] in human. In veterinary field, these studies are also in progress. Dobutamine infusion increases the frequency and intensity of movements of cardiac structures. To minimize these artifacts, wall filters were increased progressively during stress testing in the present study. And adverse effect associated with dobutamine stress testing in human has been described. Possible cardiac adverse effects are ventricular premature beats, target heart rate, and angina pectoris; possible non-cardiac adverse effects are nausea, anxiety, headache, and tremor urgency [14]. None of these was observed in this study.

Percentage of fractional shortening of the left ventricle and ejection fraction are echocardiographic indices of systolic cardiac performance. On advantage of using these indices is that they are independent of body weight [15]. Percentage of fractional shortening of the left ventricle and ejection fraction obtained from dogs at rest in this study were agreement with reference values [2] and these indices were increased with dobutamine infusion. In dogs with mitral regurgitation, usually have a supernormal left ventricular shortening fraction. But these indices were increased with dobutamine infusion that shows intact myocardial response. Accordingly, it is considered that myocardial dysfunction was not occurred in dogs with experimentally induced mitral regurgitation. Aortic valve areas at rest and at peak infusion were not significantly different so that these areas were considered unchanged during dobutamine infusion. Aortic stroke volume was greatly increased at dobutamine infusion and regurgitant fraction was decrease. Regurgitant volume at both dobutamine infusion and rest was similar because of decreased vascular resistance and increase of myocardial contractility due to pharmacologic effects of dobutamine. Regurgitant volume was not significantly changed but increase of mitral annulus stroke volume and aortic stroke volume cause reduction in regurgitant fraction. Effective regurgitant orifice was not changed significantly according that regurgitant volume was not changed. The sensitivity of dobutamine stress echocardiography to detect cardiac disease has yet to be proved. To apply this protocol in clinical field, dobutamine stress echocardiography should be performed in another experimental model or patient of early myocardial dysfunction. The aim of this study was to investigate the hemodynamic response to dobutamine infusion in dogs with mitral regurgitation. Dobutamine stress echocardiography was safe in conscious dogs with experimentally induced mitral regurgitation. Marked increase in mitral annulus inflow volume, aortic stroke volume and decrease in regurgitant fraction in quantitative Doppler examination during dobutamine infusion. Hemodynamic indices such as aortic outflow and mitral annulus stroke volume, increased regardless of mitral valve regurgitation.

In conclusion, quantitative Doppler echocardiography is a noninvasive and reliable method for detecting new hemodynamic factors, effective regurgitant orifice area. Dobutamine stress test shows that myocardial activity is intact in dogs with experimentally induced mitral regurgitation. However, it is thought that effective regurgitant orifice area is a hemodynamic nondependent factor for estimation of severity mitral regurgitation in exciting state by dobutamine.

Acknowledgment

This study was supported in part by the Research Institute of Veterinary Science, College of Veterinary Medicine, Seoul National University.

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