European Heart Journal (1999) **20,** 386–392
Article No. euhj.1998.1355, available online at http://www.idealibrary.com on IDEAL

Prevalence and significance of left ventricular outflow gradient during dobutamine echocardiography

D. Luria, M. W. Klutstein, D. Rosenmann, J. Shaheen, S. Sergey and D. Tzivoni

Department of Cardiology, Jesselson Heart Center, Shaare Zedek Medical Center, Jerusalem, Israel

Aims This study investigated the clinical and physiological significance of the dynamic left ventricle outflow gradient observed in some patients during dobutamine stress echocardiography.

Methods Three hundred and ninety-four consecutive patients completed dobutamine stress echocardiography using Doppler echocardiography to assess the presence of myocardial ischaemia and left ventricular outflow gradient. The prevalence of left ventricular outflow gradient was evaluated and correlated with echocardiographic and clinical findings. Fifteen patients with left ventricular outflow gradient during dobutamine infusion underwent exercise echocardiography for appearance of left ventricular outflow gradient.

Results Sixty-nine of 394 (17·5%) patients developed a left ventricular outflow gradient of more than 36 mmHg. In nine of them (13%) the anterior mitral valve leaflet had a systolic anterior motion. In 60 of the 69 patients (87%) there was a dynamic obstruction at the level of the papillary muscles. The mean intracavitary gradient was 75·4 (range 36–175) mmHg.

There was no correlation between the presence or absence of a dobutamine stress echocardiography-induced left ventricle outflow gradient and chest pain or shortness of breath. In patients who developed a left ventricular outflow gradient ischaemic wall motion abnormalities occurred at a significantly lower frequency during dobutamine stress echocardiography (2·9 vs 16·4% $P<0·001$).

None of the 15 patients who underwent exercise echocardiography developed significant left ventricular outflow gradient.

Conclusion Left ventricular outflow gradient occurs occasionally during dobutamine stress echocardiography examination. Its presence is of no physiological or clinical significance.
(Eur Heart J 1999; 20: 386–392)

Key Words: Dobutamine echocardiography, left ventricular outflow gradient.

Introduction

In recent years, dobutamine stress echocardiography has emerged as an accurate method for evaluation of patients with suspected or known ischaemic heart disease. Dobutamine is a beta-1 agonist with a positive inotropic and chronotropic effect, which can also cause peripheral vasodilatation and hypotension due to its partial beta-2 stimulation[1]. Pellikka and co-workers[2] were the first to describe the development of a dynamic intraventricular gradient during dobutamine stress echocardiography, but the prevalence and the physiological significance of this observation were not investigated. The authors suggested that stress-induced dynamic left ventricular intracavitary obstruction may account for clinical symptoms, such as chest pain and dyspnoea in selected patients, but this assumption has never been proved. It is unknown whether the left ventricular outflow gradient is associated with increased incidence of symptoms or with the development of new wall motion abnormalities.

Pellikka *et al.*[2] and Marcovitz *et al.*[3] noted a significant correlation between the development of a left ventricular outflow gradient and systemic hypotension, and therefore they used a normal saline infusion during dobutamine stress echocardiography. In animal experiments, dobutamine-induced left ventricular cavity obliteration was not associated with hypotension and could not be prevented by volume loading[4].

This study was performed in order to assess prevalence of left ventricular outflow gradient during

Revision submitted 22 September 1998, and accepted 7 October 1998.

Correspondence: Marc W. Klutstein, MD, Department of Cardiology, Jesselson Heart Center, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel.

0195-668X/99/050386+07 $18.00/0

dobutamine stress echocardiography and its clinical significance.

Methods

Patients

Four hundred and fifty-seven patients were referred for dobutamine stress echocardiography at Shaare Zedek Medical Center between March 1995 and March 1996. Three hundred and ninety-four of them were included in this study. Patients who were referred for a low grade dobutamine echo test for evaluation of myocardial viability (27 patients), who had an inconclusive test for technical reasons (21 patients), or a negative test with a final heart rate of less then 75% of the age-adjusted maximal rate (23 patients) were not included in the study.

There were 172 male and 222 female patients aged 27 to 87 years (mean 63·3); 186 (47·2%) of them were referred because of chest pain, 44 (11·2%) because of shortness of breath, 109 (27·7%) had known coronary artery disease and were referred for evaluation.

Fifteen of the patients with a left ventricular outflow gradient during dobutamine stress echocardiography, also underwent a submaximal exercise treadmill test according to the Bruce protocol and a continuous wave and colour Doppler examination before and within 1 min of completing the exercise test.

The study was approved by the hospital ethics committee and all patients gave their informed consent to participate in this trial.

Statistical analysis

Continuous variables' data are expressed as mean value ± SD and the unpaired two-tailed Student t-test was performed for comparative analysis. Categorical variables are expressed as a percentage. For categorical variables, comparison between groups were made using the chi-square test. Results were considered significant at $P<0·05$.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed according to a previously described protocol[5,6]. Infusion of dobutamine was begun with a dose of 5 μg . kg^{-1} . min^{-1} and increased every 3 min to 10, 20, 30, 40 and 50 μg . kg^{-1} . min^{-1}. Blood pressure and a 12-lead ECG were recorded at baseline, at the end of each stage of dobutamine infusion and during recovery. The ECG was monitored throughout the examination. If the target heart rate was not achieved at the peak of dobutamine infusion, intravenous atropine (0·5–2·0 mg) was added.

A two-dimensional echo-Doppler was performed in parasternal and apical views at each stage of the protocol. Dobutamine stress echocardiography was terminated if the target heart rate was achieved, if new regional wall motion abnormalities developed accompanied by severe anginal pain or if significant haemodynamic changes, significant supraventricular or ventricular arrhythmias or severe adverse effects were observed. Hypotension during the test was defined as a drop in the systolic blood pressure of $\geq$20 mmHg from the resting blood pressure. A significant left ventricular outflow gradient was defined as a new gradient of $\geq$36 mmHg.

Exercise echo

Fifteen patients with a significant left ventricular outflow gradient and a test negative for ischaemia who were able to perform a treadmill exercise test were selected for exercise echo-Doppler study. None of them had demonstrated systolic anterior motion of the anterior mitral leaflet during the echo-dobutamine test. The exercise echo-Doppler study was performed within 6 months of the echo-dobutamine test and no changes occurred in the clinical status and functional capacity of the patients between the two tests. A treadmill exercise test was performed according to the standard Bruce protocol. Continuous wave and colour Doppler examination of left ventricular outflow tract were recorded from the apical four chamber view before and immediately after exercise. The left ventricular outflow gradient was measured within 60 s of completing the exercise test.

Echocardiographic analysis

Echocardiograms were recorded on S-VHS video cassettes and analysed by a highly experienced cardiologist. The left ventricle was divided into 16 segments for evaluation of the regional wall motion. Ischaemia was defined as a new wall motion abnormality in two or more adjacent segments. The left ventricular outflow velocity was measured at peak dobutamine stress echocardiography by continuous wave Doppler. The left ventricular outflow gradient was calculated from the velocity by the modified Bernoulli equation, as incorporated in the software of the echo-Doppler system. If the left ventricular outflow gradient was associated with systolic anterior motion on the 2D or M-mode echocardiogram, the obstruction was defined as localized at the left ventricular outflow tract. The obstruction was defined as a mid-cavitary obstruction if there was no systolic anterior motion.

Results

Of the 394 consecutive patients who underwent dobutamine stress echocardiography, 69 (17·5%) developed

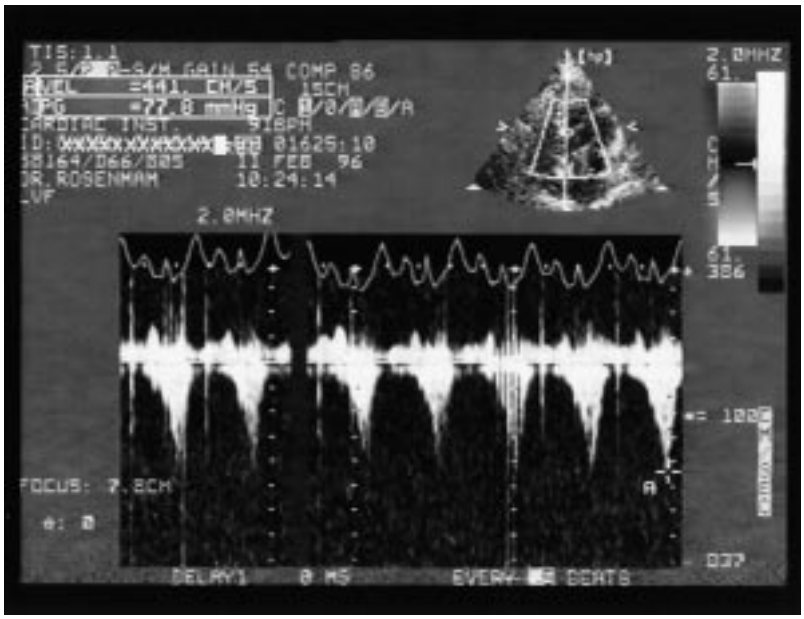

Figure 1 **Continuous wave Doppler velocity tracing from the apical four chamber view at the peak of the dobutamine infusion. Note 'late peaking' of the ventricular outflow gradient characteristic of dynamic cavity obstruction.**

Table 1 Characteristics of the patients with and without left ventricular outflow gradient (LVOTG)

	LVOTG n=69	No LVOTG n=325	*P*
Mean age (years)	65·5	61	ns
Males	22 (32%)	150 (45·2%)	$P<0·05$
Reason for examination			
Chest pain	41 (59·4%)	145 (44·7%)	$P<0·05$
Exertional dyspnoea	11 (15·9%)	33 (10·2%)	ns
Known coronary artery disease for evaluation	6 (8·7%)	103 (31·7%)	$P<0·001$
Risk stratification before operation	2 (2·9%)	—	
Others	9 (13%)	34 (10·5%)	ns
Echocardiography			
Asymmetrical septal hypertrophy	23 (33%)	55 (16·9%)	$P<0·002$
Septum thickness (cm)	$1·20 \pm 0·17$	$1·13 \pm 0·19$	ns

an intraventricular gradient ≥ 36 mmHg at the peak of dobutamine infusion, with a range from 36 to 187 mmHg (mean: 75·4 mmHg) (Fig. 1).

Clinical and echocardiographic characteristics of the patients with and without a left ventricular outflow gradient are summarized in Table 1. A left ventricular outflow gradient developed more frequently in women (68%) than in men (32%, $P<0·01$). The number of patients who were referred to dobutamine stress echocardiography for evaluation of unexplained chest pain or dyspnoea was significantly greater in the group with a left ventricle outflow gradient (75·3% vs 54·9%, $P<0·002$). Prevalence of asymmetrical septal hypertrophy was significantly greater (33%) in the group with a left ventricle outflow gradient then in the group without (16·9%), $P<0·002$. The mean septal thickness was not significantly higher in the group with than without a left ventricular outflow gradient ($-1·20 \pm 0·17$; $-1·13 \pm 0·19$ ($P>0·05$, respectively)). There was no difference in the incidence and severity of mitral regurgitation in the two groups. Left ventricular function at rest was normal on two-dimensional echocardiographic examination in all the patients who developed a left ventricle outflow gradient.

Table 2 summarizes the results of dobutamine stress echocardiography on patients with and without a left ventricular outflow gradient. Sixty one (88%) of the patients who developed a left ventricle outflow gradient received 50 $\mu g \,.\, kg^{-1} \,.\, min^{-1}$ compared to 187 (57·5%) of the patients without a left ventricular outflow gradient ($P<0·0001$). Atropine was given slightly more frequently to the left ventricular outflow gradient group (58 vs 52%), but all patients in both groups achieved target heart rate. There was no significant difference between

Table 2 Dobutamine Stress Echo results

	LVOTG n=69	No LVOTG n=325	*P*
Positive (new wall motion abnormality)	2 (2·9%)	100 (30·8%)	*P*<0·0001
Hypotensive reaction (>20 mmHg)	8 (12%)	5 (1·5%)	*P*<0·0001
Systolic anterior motion appearance	9 (13%)	—	
Maximum dobutamine dose was achieved	61 (88%)	187 (57·5%)	*P*<0·0001
Atropine addition	40 (58%)	280 (52·9%)	*P*<0·0001
Chest pain or dyspnoea during test	11 (15·9%)	64 (19·7%)	ns

Table 3 Comparison of exercise echo and dobutamine echo (DSE)

	DSE n=69	Exercise echo n=15	*P*
Maximal heart rate (beats . min^{-1})	154 ± 19 (126–178)	143 ± 16 (119–1710)	ns
Intraventricular gradient (mmHg)	89 ± 35 (53–175)	16 ± 6 (7–30)	*P*<0·0001
Chest pain	9 (13%)	0	
Ischaemic wall motion abnormality	2 (2·9%)	0	

the groups in terms of the appearance of chest pain or dyspnoea during dobutamine stress echocardiography (15·9 vs 19·7%, $P=0·49$). Only two patients (2·9%) with a left ventricle outflow gradient compared to 100 patients (30·8%) without a left ventricular outflow gradient had evidence of ischaemic during dobutamine stress echocardiography ($P<0·0001$). One of these two patients had significant coronary artery disease and the other had a normal coronary angiogram.

Nine of the 69 patients (13%) with a left ventricular outflow gradient developed systolic anterior motion at the peak of the dobutamine infusion, with a gradient of 45 to 95 (mean 70·3) mmHg.

No significant complications or adverse effects were observed during dobutamine stress echocardiography in patients with or without intracavitary obstruction. Eight patients (12%) in the group with a left ventricle outflow gradient developed hypotension compared with five (1·5%) in the group without a left ventricular outflow gradient ($P<0·0001$). The mean intraventricular gradient was not different between patients with and without a hypotensive reaction: 74·6 mmHg vs 79 mmHg, respectively ($P>0·1$). The left ventricular dimensions and function at rest were similar in the two groups: mean left ventricular end-diastolic diameter 4·2 cm and 4·45 cm, mean left ventricular end-systolic diameter 2·45 cm and 2·6 cm, mean fractional shortening 41·8% and 41·6% with and without hypotensive reaction, respectively (all $P>0·1$).

Fifteen patients with dobutamine stress echocardiography-induced left ventricular outflow gradient also underwent exercise Doppler echocardiography. There were nine male and six female patients with a mean age of 64·1 years. None of these patients developed significant (>36 mmHg) left ventricle outflow gradient during exercise. (Table 3, Fig. 2).

Discussion

In the present study we assessed the frequency and significance of the development of the left ventricle outflow gradient during dobutamine stress echocardiography. Of the 394 consecutive patients who underwent dobutamine stress echocardiography, 69 (17·5%) developed a significant (>36 mmHg) left ventricular outflow gradient. In 60 of these 69 patients, the obstruction was localized at the papillary muscle level, and in nine of them it was associated with systolic anterior motion.

Pellikka *et al.*[2] first described the left ventricular outflow gradient in a group of 57 patients. The gradient was observed in 21% of the patients in their study who underwent dobutamine stress echocardiography. They supposed that during stress-induced adrenergic stimulation, the same phenomenon could develop, leading to increase of myocardial oxygen demand and clinical symptoms such as chest pain and exertional dyspnoea. In another study[7], 30 elderly patients without ischaemic or valvular heart disease were investigated by dobutamine stress echocardiography due to exercise-induced dyspnoea. The rest echocardiogram showed increased basal septal thickness and signs of diastolic left ventricle dysfunction. At the peak of dobutamine stress echocardiography, the systolic motion of the anterior mitral valve leaflet appeared in 80% of these patients, accompanied by significant left ventricular outflow gradient development. Notably, in both of the above studies, dobutamine echocardiography was considered an equivalent of physiological exercise. To our knowledge, there are no studies which investigate the appearance of the ventricular outflow gradient during exercise echo-Doppler.

In our study, 58·4% of the patients were referred for evaluation of chest pain or shortness of breath on

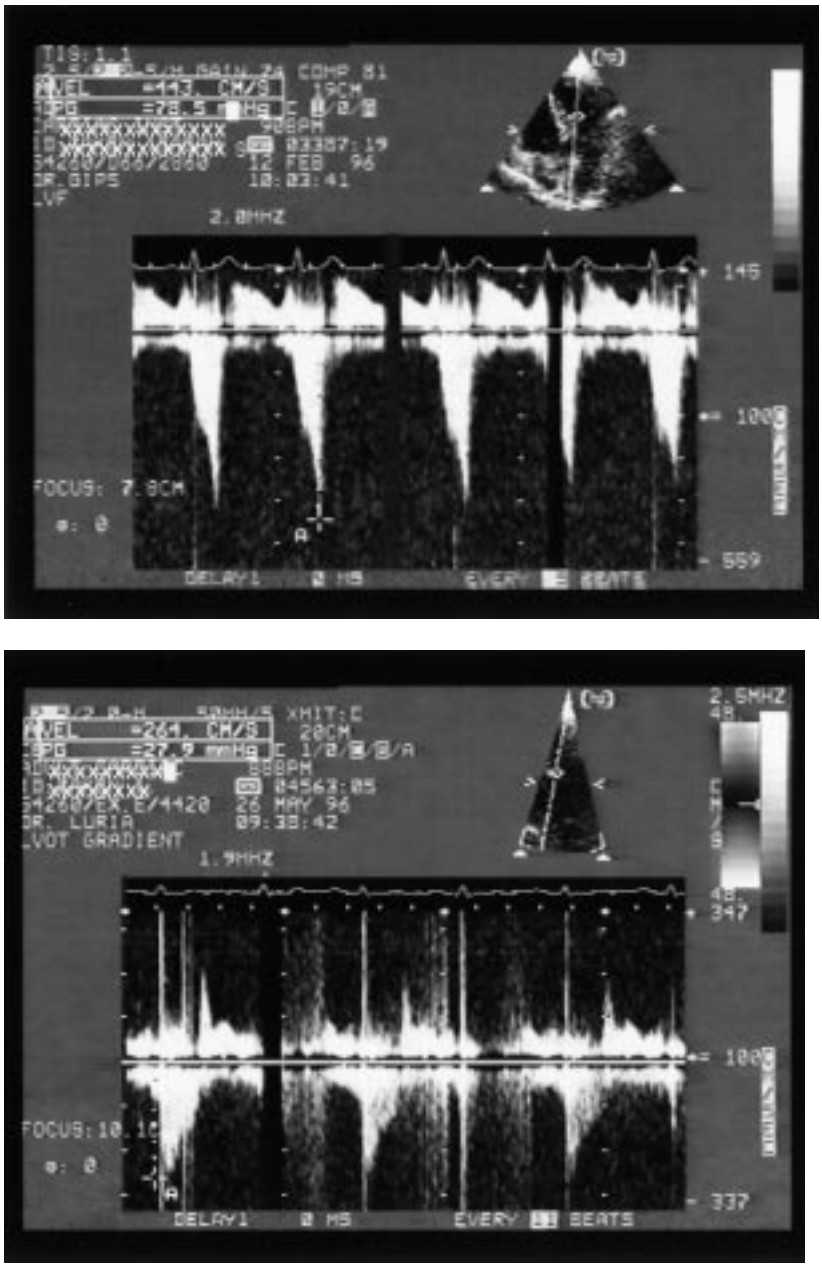

Figure 2 **Upper tracing: continuous wave Doppler velocity at the peak of dobutamine infusion showing a left ventricular outflow gradient of 78·5 mmHg. Lower tracing: recording immediately after submaximal treadmill exercise of the same patient: left ventricular outflow gradient of only 24·6 mmHg at a similar heart rate.**

effort. These symptoms were observed more frequently in patients with dobutamine stress echocardiography-induced left ventricular outflow gradient. However, during the test, patients with a left ventricular outflow gradient had the same frequency of chest pain or shortness of breath as those without a left ventricle outflow gradient, indicating that the latter is of no clinical significance. It is possible that the higher frequency of symptoms can be attributed to the increased septal thickness in this group. We also found that ischaemic wall motion abnormality was seen infrequently in patients who developed left ventricular outflow gradient as compared with patients without this development (2·9% vs 30·8%, $P<0·0001$). It is therefore likely that the incidence of coronary artery disease is less frequent in these patients than in patients without a left ventricular outflow gradient. As the symptoms of chest pain and shortness of breath were similar in the two groups it was unclear whether these symptoms could be attributed to significant left ventricular outflow gradient during exercise.

Pellikka *et al.*[2] found relative hypotension in the group of patients with dobutamine-induced intraventricular gradient and assumed, as did other authors[3], that hypotension was caused by the intraventricular obstruction at peak dobutamine infusion. In another study[8], hypotension during dobutamine stress echocardiography characteristically appeared in patients with a smaller left ventricular cavity and better ventricular function. We found that the left ventricular outflow gradient was not uncommon in patients during dobutamine stress echocardiography and was associated with hypotension. Significant hypotensive reactions developed in our study in 12% of the patients with an intraventricular gradient, as compared to 1·5% of patients without a gradient. The appearance of hypotension was not related to the severity of the left ventricular outflow gradient, which was similar in the groups with and without reduced blood pressure. In contrast to a previous study[8] we did not observe any difference in left ventricular dimensions and function in the group of patients with a hypotensive response in comparison to the group with a left ventricle outflow gradient and without a significant decrease in blood pressure. We therefore assume that the hypotension is not a result of intraventricular obstruction, as suggested previously[2,3], but is rather a result of the dobutamine-induced vasodilatation. This impression is supported by animal experiments performed by Weissman and others[4] who found that cavitary obliteration during dobutamine stress echocardiography did not lead to hypotension in dogs and saline infusion did not prevent the appearance of left ventricle outflow gradient.

Asymmetrical septal hypertrophy is a common echocardiographic finding, frequently associated with hypertension and usually not associated with systolic anterior motion of the anterior mitral leaflet or intracavitary obstruction[9]. Autopsy studies of elderly patients revealed an increased prevalence of sygmoid hypertrophy of the ventricular septum, characterized by the knob-like prominence of its basal subaortic segment[10]. It was considered as an age-related change. Some patients with this finding later developed symptomatic left ventricular outflow gradient obstruction[11] and this was defined as a special form of hypertrophic obstructive cardiomyopathy of the elderly[9]. In our study asymmetrical septal hypertrophy was present in 33% of patients with dynamic intraventricular obstruction, compared to 16·9% in those without a left ventricular outflow gradient ($P<0·001$). It is possible that this usually innocent anatomical structure contributes to the development of cavitary obstruction during more forceful contraction of the papillary muscles or the septum, induced by the positive inotropism of dobutamine. It is also not clear whether the patients developing systolic anterior motion of the mitral valve is a separate group with a mild form of inducible hypertrophic obstructive cardiomyopathy or it is again a reaction to dobutamine infusion.

In order to clarify the physiological significance of a dobutamine-induced intraventricular gradient, we performed exercise echo-Doppler examination in a subgroup of 15 patients with dobutamine stress echocardiography-induced ventricle outflow gradient. While during dobutamine echocardiography the intracavitary gradient in these patients was 89 ± 35 mmHg, none of them developed significant gradient on Doppler echocardiography after exercise. These findings indicate that the left ventricular outflow gradient during dobutamine stress echocardiography does not identify patients with cavitary obstruction under physiological condition, such as exercise. Thus dobutamine stress echocardiography-induced left ventricular outflow gradient is of no physiological importance. Therefore it is unnecessary to change the medical therapy in these patients or to discontinue diuretics and vasodilators, as was suggested by other authors[2]. This approach is used in patients with hypertrophic cardiomyopathy, but not necessary in the patients in this study.

The different response of the left ventricle to dobutamine and exercise can possibly be explained by the different mode of stimulation. Dobutamine increases myocardial contraction in association with peripheral vasodilatation. These two mechanisms may reduce the left ventricular volume and contribute to the development of the left ventricular outflow gradient, while during exercise, catecholamine-induced peripheral vasoconstriction may prevent reduction in left ventricular volumes and left ventricular outflow gradient development.

Conclusions

The left ventricular outflow gradient was observed in 17·5% of patients during dobutamine stress echocardiography. The development of a dynamic left ventricular outflow gradient during dobutamine stress echocardiography is a pharmacological phenomenon which is of no clinical importance. It is not associated with increased frequency of dobutamine-induced pain or shortness of breath or ischaemic wall motion abnormalities. Patients with a dobutamine stress echocardiography-induced left ventricular outflow gradient do not develop a left ventricular outflow gradient during exercise echocardiography.

References

[1] Drugs for the heart. Opie LH ed. Philadelphia: W. B. Saunders Company, 1994.
[2] Pellikka P, Oh J, Bailey K, Nichols B, Monahan K, Tajik A. Dynamic intraventricular obstruction during dobutamine stress echocardiography. A new observation. Circulation 1992; 86: 1429–32.
[3] Marcovitz P, Bach D, Mathias W, Shayna V, Armstrong W. Paradoxic hypotension during dobutamine stress echocardiography: clinical and diagnostic implications. J Am Coll Cardiol 1993; 21: 1080–6.
[4] Weissman N, Nidorf S, Weyman A, Picard M. Effect of hydration on cavity obliteration during dobutamine stress echocardiography. Clin Cardiol 1995; 18: 17–20.

[5] Sawada S, Segar D, Ryan T *et al*. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991; 83: 1605–14.
[6] Roger V, Pellikka P, Oh J, Miller F, Seward J, Tajik A. Stress echocardiography. Part I. Exercise echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995; 70: 5–15.
[7] Henien M, O'Sullivan C, Sutton G *et al*. Stress-Induced Left Ventricular Outflow Tract Obstruction: A Potential Cause of Dyspnea in the Elderly. J Am Coll Cardiol 1997; 30: 1301–7.
[8] Rallidis L, Cokkinos P, Tousoulis D *et al*. Comparison of Dobutamine and Treadmill Exercise Echocardiography in Inducing Ischemia in Patients With Coronary Artery Disease. J Am Coll Cardiol 1997; 30: 1660–8.
[9] Lever H, Karam R, Currie P *et al*. Hypertrophic cardiomyopathy in the elderly, distinctions from the young base on cardiac shape. Circulation 1989; 79: 580–9.
[10] Goor D, Lillehei C, Edwards J. The 'sigmoid septum': Variation in the contour of the left ventricle outlet. Am J Roentgenol Rad Therapy Nucl Med 1969; 107: 366–76.
[11] Lewis J, Maron B. Elderly patients with hypertrophic cardiomyopathy: A subset with distinctive left ventricular morphology and progressive clinical course late in life. J Am Coll Cardiol 1989; 13: 36–45.