

Dynamic left ventricular outflow tract obstruction evoked by exercise echocardiography: prevalence and predictive factors in a prospective study

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KEYWORDS

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Aims In patients without hypertrophic obstructive cardiomyopathy (HOCM), dynamic left ventricular outflow tract obstruction (DLVOTO) can cause ischaemia. Little is known about incidence and predictors of DLVOTO in patients without HOCM.

Methods and results In 300 patients referred for exercise echocardiography, assessment of DLVOTO at rest and with Valsalva and of the presence of systolic anterior motion of the mitral valve leaflets (SAM) was performed. Within 90 s post-exercise, wall motion, SAM, and DLVOTO were assessed again. A significant DLVOTO was defined as late-peaking Doppler velocity of ≥ 2.5 m/s (25 mmHg). Excluded were 7 patients with HOCM and 13 with inadequate image quality. There were 280 patients, aged 64(11) years. Coronary artery disease was found in 38% of patients; 44% were receiving beta-blocker therapy and 35% had hypertension. At rest, ejection fraction was $59 \pm 9\%$; left ventricular hypertrophy (LVH) was present in 21%, SAM in 16%, DLVOTO ≥ 25 mmHg at rest in 0.7%, and with Valsalva in 3%. At peak, echocardiographic signs of ischaemia occurred in 44%, and significant DLVOTO in 5% (13 patients). By multivariate analysis, it was found that independent predictors of significant DLVOTO at peak were chordal SAM at peak, smaller left ventricle at end-systole, higher systolic blood pressure at peak, younger age and increased septal wall thickness. Significant DLVOTO was a possible cause of symptoms and/or ischaemia in at least 6 of the 13 patients.

Conclusion Haemodynamically significant exercise-induced DLVOTO can occur without HOCM. Chordal SAM at peak, small, hyperdynamic left ventricles, increased septal wall thickness, and younger age are the best predictors.

Introduction

Dynamic left ventricular outflow tract obstruction (DLVOTO) is a typical feature of hypertrophic obstructive cardiomyopathy (HOCM) occurring in almost 50% of patients with hypertrophic cardiomyopathy. However, it has also been described that DLVOTO occurred in patients with hypertensive heart disease,¹ pheochromocytoma or due to catecholamine treatment,^{2,3} with acute myocardial infarction,⁴ prior mitral valve repair^{5,6} or aortic valve replacement, with pericardial effusion, or dehydration. It has also been proposed as a mechanism for Tako-Tsubo cardiomyopathy⁷ or as a reason

for subendocardial ischaemia causing exercise-induced dyspnea.⁸

During dobutamine stress echocardiography, DLVOTO can occur in 17–43% patients and is not predictive of HOCM.^{9–13} And also, it may lead to blood pressure drop, ischaemia or have prognostic implications.^{9–15} During treadmill stress echocardiography, DLVOTO is rare: in a population of 2213 patients, it occurred in 1.8% of patients; most had LV hypertrophy (77%).¹⁶ In another study with 211 patients, it was found that DLVOTO occurred in 13% patients with gradients ranging from 25 to 53 mmHg, and appeared to contribute to angina or dyspnea.¹⁷

There are few data on prevalence of exercise-induced DLVOTO or its pre-disposing factors. Therefore, the goal of our study was to assess the prevalence and predictive factors of DLVOTO.

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Methods

Study population

Consecutive patients referred for treadmill stress echocardiography between July 2005 and November 2006 were prospectively included. Patients in whom image quality was diminished and who received an echocardiographic contrast agent were not included in the study as this would not have allowed the assessment of mitral regurgitation, or SAM post-exercise.

Among 300 patients, 20 patients were excluded: 7 patients with known hypertrophic cardiomyopathy (by family history, genetic analysis, etc) or suspected hypertrophic cardiomyopathy with otherwise unexplained left ventricular hypertrophy, and 13 patients in whom image quality post-exercise was diminished and in whom DLVOTO could not reliably be assessed within 90 s post-exercise.

Transthoracic echocardiography

A complete two-dimensional and Doppler echocardiographic exam was performed in each patient immediately prior to exercise echocardiography. All exams were performed with the patient in the left lateral decubitus position using an Acuson Sequoia 512 machine. Left ventricular (LV) ejection fraction was determined using biplane Simpson's method. LV mass was calculated according to Devereux.¹⁸ LV hypertrophy was defined as ≥ 134 g/m² in men and ≥ 110 g/m² in women.

Dynamic left ventricular outflow tract obstruction was sought at rest and during the performance of a Valsalva manoeuvre. A significant DLVOTO was defined as a late peaking systolic gradient of at least 25 mmHg. Colour Doppler was used to verify that the obstruction was indeed in the outflow tract and not in the mid-cavity. The presence of systolic anterior motion of the mitral valve or mitral chordae was noted. Chordal SAM was defined as SAM of the mitral valve chordae without significant anterior motion of the mitral valve leaflets. M-mode tracings were not used for the assessment of SAM. The degree of mitral regurgitation was graded as Grade I–IV.¹⁹

Exercise echocardiography

Treadmill stress echocardiography was performed using the Bruce or modified Bruce protocol with 3 min stages.²⁰ Cardiac medications were continued. With continuous wave (CW) Doppler, DLVOTO was measured at baseline, after at least 10 s of a Valsalva manoeuvre, and post-exercise, immediately after acquisition of two-dimensional images with the CW Doppler parallel in the LV outflow tract. Two-dimensional images were acquired within 60 s post-exercise followed immediately by the assessment of the dynamic gradient within the LV outflow tract with CW Doppler and the presence or absence of SAM. A stopwatch was used to ascertain that image

acquisition was completed by 90 s; otherwise, the patient was excluded (13 patients, see above). By color flow Doppler, the degree of mitral regurgitation was also noted after exercise to notice a change. The presence of echocardiographic ischaemia was defined as new or worsening wall motion abnormality in at least one segment using a 17-segment model.²¹ An ECG positive for ischaemia was defined as ≥ 0.1 mV ST-segment depression 80 ms after the J point in the ECG. Symptoms of the patient were noted. Heart rate and blood pressure response were measured at rest, throughout exercise and during the first 6 min of recovery.

Statistical analysis

Categorical variables were compared using χ^2 analysis or Fisher's exact test. Continuous variables were expressed as mean \pm 1 SD and compared using the Mann–Whitney test. Step-wise logistic regression analysis by forward selection was performed on those parameters significantly different on univariate analysis to identify independent predictors of DLVOTO developing during exercise echocardiography. All statistical analysis was two-tailed with a *P*-value of <0.05 to indicate statistical significance. The Statview software (version 5.0, SAS Inc. Cary, NC 27513, US.) was used for all analysis.

Results

There were 280 patients in our study group [188 males (67%)]. Clinical characteristics and the cardiac medications are shown in *Table 1*. The intake of at least one cardiac medication was reported by 180 patients (64%). Only one patient was taking digoxin, this was not included in further analysis.

Table 2 shows the echocardiographic parameters at rest comparing patients with and without DLVOTO. Patients with DLVOTO with exercise had a higher LV shortening fraction, smaller LV end-diastolic and end-systolic diameters, and increased septal and posterior wall thickness, and more often had chordal SAM at rest. DLVOTO with and without Valsalva was also much more common in patients with significant DLVOTO after exercise.

In *Table 3*, data of exercise echocardiography are shown. Patients who had DLVOTO at peak had a higher heart rate and higher systolic blood pressure with exercise, but there was no difference in the occurrence of symptoms or signs of ischaemia at echocardiography or in the ECG. Chordal SAM at peak was significantly more common in patients with significant DLVOTO.

A blood pressure drop of 18 ± 15 mmHg was observed in 11 patients: in 10 of these 11 patients, the blood pressure

Table 1 Clinical characteristics and cardiac medication of the 280 patients

	All (n = 280)	DLVOTO \geq 25 mmHg after exercise (n = 13)	No significant DLVOTO after exercise (n = 267)	<i>P</i> -value
Age, years	64 \pm 11	59 \pm 11	64 \pm 11	0.14
Male gender	188 (67%)	13 (100%)	175 (66%)	0.006
Hypertension	97 (35%)	5 (38%)	92 (34%)	0.77
BMI, kg/m ²	26 \pm 4	26 \pm 4	26 \pm 4	0.60
Known CAD	107 (38%)	2 (15%)	105 (39%)	0.14
Sinus rhythm	264 (94%)	13 (100%)	251 (94%)	1.0
Beta blocker	123 (44%)	3 (23%)	120 (45%)	0.16
ACEI/ARB	101 (36%)	3 (23%)	98 (37%)	0.39
Diuretic	71 (23%)	2 (15%)	69 (26%)	0.53
CCA	37 (13%)	2 (15%)	35 (13%)	0.68

BMI, body mass index; CAD, coronary artery disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CCA, calcium-channel antagonists.

Table 2 Comparison of echocardiographic parameters at rest in patients with and without dynamic left ventricular outflow tract obstruction

	All (n = 280)	DLVOTO \geq 25 mmHg after exercise (n = 13)	No significant DLVOTO after exercise (n = 267)	P-value
Ejection fraction, %	59 \pm 9	64 \pm 8	59 \pm 9	0.06
Shortening fraction, %	39 \pm 10	45 \pm 7	38 \pm 9	0.005
LVEDD, mm	46 \pm 6	42 \pm 3	46 \pm 6	0.007
LVESD, mm	29 \pm 14	23 \pm 3	30 \pm 14	0.0005
LVMMI, g/m ²	101 \pm 33	108 \pm 24	101 \pm 33	0.32
Septum, mm	12 \pm 3	14 \pm 2	12 \pm 3	0.006
Posterior wall, mm	10 \pm 2	11 \pm 2	10 \pm 2	0.02
Left ventricular hypertrophy	58 (21%)	5 (38%)	53 (20%)	0.15
Mitral regurgitation				0.99
None/trivial	235 (83%)	11 (85%)	224 (83%)	
Mild	41 (14%)	2 (15%)	39 (14%)	
Moderate	5 (2%)	0	5 (2%)	
Severe	2 (1%)	0	2 (1%)	
Aortic stenosis ^a , any	31 (11%)	1 (8%)	30 (11%)	1.0
Chordal SAM at rest	45 (16%)	8 (62%)*	37 (14%)	0.0002
DLVOTO \geq 25 mmHg at rest	2 (1%)	2 (15%)	0	0.002
DLVOTO \geq 25 mmHg Valsalva	9 (3%)	3 (23%)	6 (2%)	0.006
Elongated/anomalous chordae	7 (3%)	0	7 (3%)	1.0

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular endsystolic diameter; LVMMI, left ventricular muscle mass index; VLH, left ventricular hypertrophy; DLVOTO, dynamic left ventricular outflow tract obstruction; systolic anterior motion.

^aAortic stenosis was mild in 25 patients and moderate in 6 patients, no patient had severe aortic stenosis.

Table 3 Comparison of exercise echocardiography data

	All (n = 280)	DLVOTO \geq 25 mmHg after exercise (n = 13)	No significant DLVOTO after exercise (n = 267)	P-value
METS	9.1 \pm 2.5	10.3 \pm 3.0	9.1 \pm 2.4	0.22
HR rest, bpm	68 \pm 12	74 \pm 12	78 \pm 12	0.08
HR peak, bpm	142 \pm 21	157 \pm 19	141 \pm 21	0.01
BP systolic rest, mmHg	144 \pm 19	148 \pm 19	144 \pm 19	0.43
BP systolic peak, mmHg	189 \pm 28	213 \pm 29	188 \pm 30	0.006
ECG positive for ischaemia	108 (39%)	6 (46%)	102 (38%)	0.84
Echo positive for ischaemia	124 (44%)	6 (46%)	118 (44%)	1.0
EF at peak, %	63 \pm 12	71 \pm 8	63 \pm 12	0.005
Angina	29 (10%)	2 (15%)	27 (10%)	0.64
Dyspnea	123 (44%)	3 (23%)	120 (45%)	0.16
Increase in MR	30 (11%)	1 (8%)	29 (11%)	0.52
Chordal SAM at peak	59 (21%)	10 (77%)	49 (18%)	<0.0001

HR, heart rate; BP, blood pressure; MR, mitral regurgitation; SAM, systolic anterior motion.

drop was associated with ischaemia ($P=0.003$). In 1 patient, the cause of blood pressure drop was unclear. None of the patients with a blood pressure drop had DLVOTO of \geq 25 mmHg. Univariate and multivariate predictors of significant DLVOTO at peak are shown in *Table 4*.

Significant independent predictors of DLVOTO at peak were chordal SAM at peak, a smaller LV end-systolic diameter, younger age, increased septal wall thickness, and a higher systolic blood pressure at peak.

The 13 patients with significant DLVOTO are shown in *Table 5*. Dyspnea occurred in six patients and angina occurred in two patients. Coronary angiography was performed in nine patients: in six of the nine patients, coronary anatomy was normal despite echocardiographic ischaemia (four patients) or dyspnea (two patients) which might have been caused, therefore, by DLVOTO. On the other hand, Patient 88 had 50% LAD stenosis and no echocardiographic signs of ischaemia despite DLVOTO of 100 mmHg.

Figure 1A–C and Figure 2 show the pertinent echocardiographic images of Patient 35. His left ventricular end-diastolic diameter was 4.3 cm, the shortening fraction 60%, the gradient in the LV outflow tract at rest 8 mmHg, after Valsalva 77 mmHg (Figure 2), and after exercise 39 mmHg (Figure 1C). Despite echocardiographic signs of ischaemia, he had normal coronary arteries; therefore, ischaemia might have been due to DLVOTO.

Table 4 Summary of univariate and multivariate predictors of significant DLVOTO with exercise

	P-values of univariate analysis	P-values, OR with 95% CI multivariate analysis
Chordal SAM peak	<0.0001	0.0009, OR 15.4 (95% CI, 3.1–77.9)-
Chordal SAM rest	0.0002	
LVESD (mm)	0.005	0.003, OR 22.6 (2.9–177.7)
EF peak (%)	0.005	
Shortening fraction (%)	0.005	
DLVOTO Valsalva	0.006	
Septal wall thickness (mm)	0.006	0.006, OR 0.004 (0.0006–0.20)
Male gender	0.006	
Systolic BP, peak	0.006	0.03, OR 0.97 (0.95–1.0)
LVESD (mm)	0.007	
Heart rate, peak	0.01	
Posterior wall thickness (mm)	0.02	
EF rest (%)	0.06	
Age (years)	0.14	0.004, OR 1.15 (1.05–1.27)
LVH	0.16	

EF, ejection fraction; DLVOTO, dynamic left ventricular outflow tract obstruction; LVESD, left ventricular end-diastolic diameters; LVH, left ventricular hypertrophy; BP, blood pressure; CI, confidence interval; OR, odds ratio.

Discussion

Our data show that exercise-induced DLVOTO can occur during exercise echocardiography even in patients without HOCM. Predictive factors include chordal SAM at peak, small left ventricles, younger age, higher systolic blood pressure post-exercise, and increased septal wall thickness. SAM of the mitral valve chordae at peak is the best predictor. DLVOTO may be a cause for myocardial ischaemia or symptoms which may be missed by other stress imaging methodologies, including nuclear perfusion imaging or magnetic resonance imaging.

Aetiology of dynamic left ventricular outflow tract obstruction

Systolic anterior motion of the anterior and rarely posterior mitral valve leaflet as well as asymmetric septal hypertrophy are the main components of DLVOTO. This is a typical feature of hypertrophic obstructive cardiomyopathy.²² There, considerable hypertrophy of the basal septum has been described to be the primary feature.^{23,24} Other factors responsible for DLVOTO in HOCM include decreased LV outflow tract size, anterior displacement of the anterior mitral valve leaflet, malposition of the papillary muscles, enlarged, elongated mitral valves, and increased ejection velocity.²⁵ However, DLVOTO has also been described in the absence of asymmetric septal hypertrophy^{26,27} in a hyperdynamic state with high normal ejection fraction, in the presence of abnormal insertions of the mitral valve or reduced septum to mitral valve distance.²⁶ SAM limited to the mitral valve chordae (chordal SAM) does not cause an increased LV outflow tract velocity,²⁸ but reflects in most patients a hyperdynamic state which makes the occurrence of DLVOTO more likely.²⁹ We excluded all patients with typical features of HOCM and most patients with DLVOTO at peak had septal wall thickness of ≤ 15 mm; however, many of these patients had high normal ejection fractions reflecting a hyperadrenergic state.

Table 5 Characteristics of the 13 patients with DLVOTO of ≥ 25 mmHg with exercise

Patient no.	Age (years)	LVH	SF (%)	EF peak	Septum (mm)	ECG ischaemia	DLVOTO (mmHg)	Echo ischaemia	Angina	Dyspnea	Coronary anatomy
5	41	No	51	75	14	No	30	No	No	Yes	NA
35	61	No	60	80	13	No	39	Yes	No	Yes	Normal
46	43	No	43	75	11	Yes	28	No	No	No	NA
66	54	No	43	80	11	No	25	Yes	No	No	CAD
78	71	No	45	60	16	Yes	25	Yes	No	No	CAD
88	48	No	43	70	11	Yes	100	No	No	No	CAD
115	61	No	50	65	12	Yes	30	Yes	Yes	No	Normal
120	54	Yes	38	70	15	No	30	No	No	No	NA
147	69	Yes	40	76	15	No	55	Yes	No	Yes	Normal
166	56	Yes	44	70	12	No	80	No	No	No	CAD
231	69	Yes	33	55	16	Yes	50	Yes	Yes	Yes	CAD
252	66	Yes	49	70	19	No	46	Yes	No	Yes	Normal
277	75	Yes	51	80	16	Yes	43	No	No	Yes	NA

LVH, left ventricular hypertrophy; SF, shortening fraction; EF, ejection fraction; ECG, electrocardiogram; NA, not available; CAD, coronary artery disease.

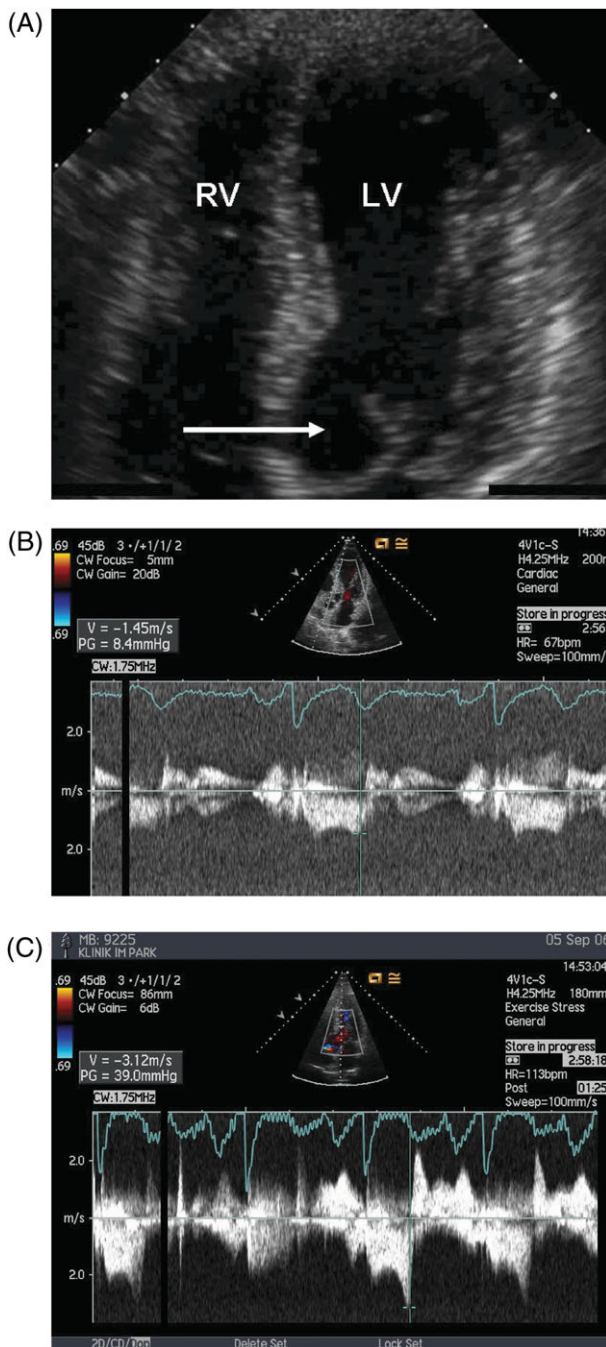


Figure 1 Example of echocardiographic findings in Patient 35, Table 6 with a gradient at rest, after Valsalva and with exercise. (A) Apical four-chamber view showing chordal SAM of the mitral valve (arrow). LV, left ventricle; RV, right ventricle. Septal wall thickness was 1.3 cm, posterior wall 1 cm, left ventricular ejection fraction 78%, shortening fraction 60%. (B) Gradient in the LVOT at rest of only 8 mmHg. (C) Gradient in the left ventricular outflow tract after exercise of 39 mmHg at heart rate of 113 bpm.

Left ventricular outflow tract obstruction as the cause of symptoms

Dynamic left ventricular outflow tract obstruction has been described as a cause of angina in various papers. Sharma *et al.*³⁰ described DLVOTO as the cause for angina in 26% of patients with end-stage renal disease undergoing

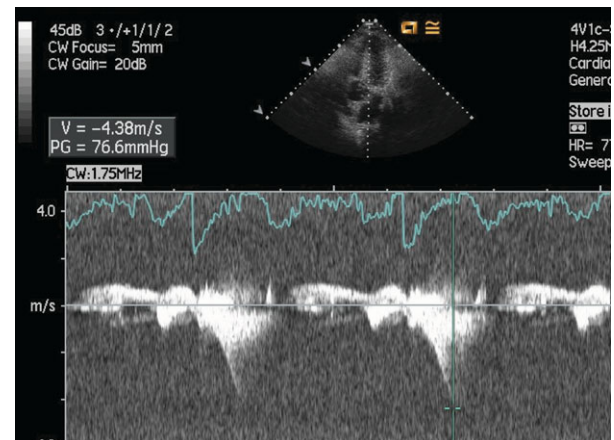


Figure 2 Gradient in the left ventricular outflow tract at rest after a Valsalva manoeuvre with a gradient of 77 mmHg.

dobutamine stress echocardiography: these patients characteristically had smaller LV cavity size and increased LV shortening fraction. DLVOTO during dobutamine stress echocardiography can also be associated with a blood pressure drop,⁹ cause symptoms or ischaemia. In 23% of 237 patients undergoing dobutamine stress echocardiography, dynamic obstruction midcavitary or the outflow tract during the infusion was an independent predictor of chest pain, syncope, and/or near syncope during a 31 ± 13 months follow-up. There has been a report of a 42-year-old man with angina and 2 mm ST depression, normal coronary arteries but DLVOTO of >144 mmHg with both treadmill exercise and dobutamine infusion.³¹ Thus, dobutamine or exercise-induced LV outflow tract obstruction can be prognostically significant.

In our patients, DLVOTO was also an unexpected cause of symptoms or myocardial ischaemia in six patients. This infrequent aetiology of ischaemia might have been missed had only coronary angiography and/or another modern cardiac evaluation with magnetic resonance imaging or nuclear perfusion imaging been performed.

Dynamic left ventricular outflow tract obstruction during catecholamine excess

The higher systolic blood pressure, chordal SAM, and younger age in our patients with DLVOTO might reflect a hyperadrenergic state. Recently, DLVOTO has been described to occur during catecholamine treatment.^{2,3} One of these reports described two patients with only mild hypertrophy of the basal septum (12 mm) with haemodynamic deterioration in the context of catecholamine treatment.² One of the pathophysiologies described for Tako-Tsubo syndrome also may include DLVOTO.^{7,32} Typical of this syndrome are elevated catecholamine levels.³³ None of our patients with exercise-induced DLVOTO had a history of Tako-Tsubo syndrome. Therefore, we do not know if routine assessment of DLVOTO evoked by exercise might help to identify patients prone to develop this syndrome. Another example of catecholamine excess is pheochromocytoma; a patient with pheochromocytoma and markedly increased mitral regurgitation during the Valsalva manoeuvre with LV hypertrophy and DLVOTO was recently described.³⁴

Limitations

The number of patients with significant exercise-induced DLVOTO of ≥ 25 mmHg was small (13 patients, 5%). Coronary angiography was not performed routinely in our patients; therefore, the impact of coronary artery disease on the development of DLVOTO cannot be determined. Although rare cases of DLVOTO have been described in patients with severe ischaemia in the left anterior descending artery territory,³⁵ none of our patients seemed to fit that category.

Post-exercise imaging as it is usually performed in treadmill stress echocardiography might lead to underestimation of the degree of DLVOTO. Even in the current study, the gradients were likely underestimated as in the first 60 s only two-dimensional images were acquired for the determination of the presence of ischaemia. Stress echocardiography with continuous imaging during stationary bicycle exercise might be preferable to determine the true incidence of DLVOTO during physical exercise.

At rest or after Valsalva, none of the patients had midcavitary obstruction; DLVOTO was limited to the LV outflow tract. Post-exercise, time was so limited for image acquisition, that it can not be excluded that part of the obstruction was midcavitary as well and not only in the left ventricular outflow tract as visualized by color Doppler imaging.

Conclusions

Significant exercise induced DLVOTO defined as a gradient of at least 25 mmHg can occur but is rare in patients without HOCM. Predictive factors include chordal SAM, small, hyperdynamic left ventricles, younger age, and DLVOTO after Valsalva. SAM of the mitral valve chordae at peak is the best predictor. In patients with unexplained dyspnea or ischaemia occurring in the absence of coronary artery disease, exercise induced DLVOTO should be excluded.

Conflict of interest: none declared.

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