Int J Cardiovasc Imaging (2012) 28:1023–1033
DOI 10.1007/s10554-011-9917-z

ORIGINAL PAPER

Left ventricular cavity obliteration during dobutamine stress echocardiography in diabetic patients

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Received: 27 December 2010 / Accepted: 21 June 2011 / Published online: 6 July 2011

Abstract Prevalence of dynamic left ventricular outflow tract obstruction (DLVO) during dobutamine stress-echo (DSE) seems disproportionally high among diabetic patients. We retrospectively identified 212 diabetic (D+) and 212 non diabetic (D−) subjects, who underwent DSE for suspected coronary artery disease (CAD); we evaluated DSE-induced DLVO prevalence and correlates. During DSE, 105 patients in D+ (50%) and 83 in D− group (39%, $P = 0.032$) developed a DLVO, with similar maximum gradient (94 ± 49 mmHg in D+ vs. 86 ± 49 mmHg in D−, P = NS). D+ and D− patients with DLVO showed reduced LV end-diastolic and end-systolic dimension. Compared with diabetic subjects without DLVO, diabetic patients with DLVO had higher left ventricular (LV) ejection fraction (EF), lower LV mass index; diastolic function was normal in a higher proportion of cases. Non diabetic patients with moderate or severe DLVO had higher LV EF compared with patients without DLVO. At multivariate analysis, in D+ patients, the only independent predictor was a smaller LV end-diastolic diameter (HR 0.779, CI 0.655–0.926, $P = 0.005$); in D− patients lower age (HR 0.878, CI 0.806–0.957, $P = 0.003$), higher LV EF (HR 1.087, CI 1.003–1.177, $P = 0.042$) and lower peak WMSI (HR 0.017, CI 0.001–0.325, $P = 0.007$) were associated to presence of DLVO. In D+ patients, during a median follow-up of 924 ± 134 days, we observed 11 new cardiac events, only 1 in patients with DLVO ($P = 0.0041$). DSE-provoked DLVO had a very high prevalence in patients evaluated for suspected CAD, especially among diabetic patients; echocardiographic predictors were a reduced LV dimension in D+ and a preserved systolic function, both at rest and at peak stress, in D− patients.

Keywords Diabetes · Dobutamine stress echocardiography · Dynamic left ventricular obstruction

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Introduction

Dobutamine stress-echocardiography (DSE) is an established tool for diagnostic and prognostic assessment [1] of patients with known or suspected coronary artery disease (CAD); its diagnostic and prognostic value has been repeatedly confirmed also in special populations, such as diabetic subjects [2–4], elderly people [5, 6], patients with low-gradient aortic stenosis

[7, 8] and patients with left ventricular (LV) systolic dysfunction [9].

In a proportion of about 20% of patients, dobutamine administration evokes an exaggerated contractile response, with a dynamic LV outflow tract obstruction (DLVO) and development of an intra-ventricular pressure gradient [10, 11]: predisposing factors seem to be female sex, small LV dimension and a preserved LV global systolic function. In patients without CAD, DLVO prevalence seems to be significantly higher [12, 13]; although from a prognostic point of view, DLVO yields a excellent value, because it seems to indicate a fully preserved LV contractile reserve, it has been reported a reduction in diagnostic accuracy, especially in presence of a coronary one-vessel disease [10].

Among diabetic patients, CAD represents the main cause of morbidity and mortality; moreover, when symptoms appear, coronary involvement is often too severe to allow an effective treatment [14]. American Diabetes Association defined a list of criteria to select diabetic patients who would undergo a screening test for CAD [15], alternatively with DSE or myocardial perfusion scintigraphy. However, in a limited series of diabetic patients undergoing DSE for CAD screening, a disproportionally high prevalence of DLVO has been previously reported [16].

Aim of this study was to verify prevalence and clinical and echocardiographic correlates of DLVO DSE-induced in a population of diabetic and non-diabetic subjects with suspected CAD.

Methods

Study patients

Between October 2006 and October 2007, 212 consecutive diabetic subjects (D+ group) underwent DSE for CAD screening, according to the recommendations of American Diabetes Association [15]. Among the other patients who performed a DSE in our Ambulatory from January 2003 to October 2007, a control group (D− group) was selected, identifying 212 non-diabetic subjects, with suspected CAD, who underwent DSE for chest pain evaluation or preoperative assessment. All patients gave their informed consent and the study is consistent with the principles of the Declaration of Helsinki of clinical research involving human subjects.

At the time of DSE we collected data about previous clinical history, level of glicate hemoglobin (HbA1c) as an indicator of metabolic control, presence of diabetic complications and current therapy, including cardiovascular and diabetic treatment. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg or the use of antihypertensive medications; patients were considered to have dyslipidemia if their total cholesterol was $\geq$200 mg/dl or if they were receiving lipid-lowering-medications. Smoking history was considered positive both for current and previous smokers. Presence of diabetic treatment indicated both insulin and/or oral agents.

Dobutamine stress protocol

B-blockers therapy was withheld the day before the examination. After the baseline echocardiogram (Sequoia, Siemens, Mountain View, CA, USA), we started the intravenous infusion of incremental doses of dobutamine beginning with low doses (LD) (5 and 10 μg/Kg/min, each stage for 3 min), followed by high doses (HD) (20, 30 and 40 μg/Kg/min, each stage for 3 min), during continuous echocardiographic and electrocardiographic monitoring and blood pressure measurement at the end of each stage [1]. Atropine (0.25 mg/min until maximum dose of 1 mg) was infused intravenous to achieve the target heart rate (85% of 220-age) in patients with sub-maximal response by dobutamine infusion alone all patients underwent DSE according to standard protocol. Test end-points were achievement of target heart rate, positive response for ischemia as development of new asynergia in two or more myocardial segments, excessive increase (systolic blood pressure, SBP, >240 mmHg) or significant reduction of blood pressure (more than 40 mmHg than preceding phase o SBP <90 mmHg), repetitive ventricular or supraventricular ectopy and development of intolerable side effects. If the patients developed inducible ischemia, propranolol was infused in incremental doses of 0.5 mg, until symptoms, ECG and echocardiographic modifications resolved.

During routine exams, in case of a hyperkinetic response, at baseline and during the last minute of each high dose (HD) stage, intraventricular systolic flow was measured by continuous wave Doppler. Dobutamine-induced DLVO was defined as appearance of an intraventricular flow acceleration of at least 3 m/s, with an abnormal shape and a maximum

velocity in late systole, without anterior motion of the mitral leaflets. With color-Doppler flow mapping, the LV obstruction was located and differentiated from any mitral regurgitation; maximum gradient was calculated from maximal velocity by the modified Bernoulli equation. On the basis of maximum gradient, patients were divided in three subgroups: no DLVO, in absence of any gradient or with a gradient up to 35 mmHg, moderate DLVO with a gradient included between 36 and 65 mmHg and severe DLVO for a maximum gradient higher than 65 mmHg.

Left ventricular end-diastolic and end-systolic dimensions were measured from 2D guided Mmode, whenever possible, or from 2D parasternal long axis view. Left ventricular (LV) volumes were measured according to Simpson's Rule method and LV ejection fraction (EF) was calculated from such volume measurements. LV mass was calculated according to the formula of American Society of Echocardiography [17] and it was indexed by height$^{-2.7}$ (LVMH). LV relative wall thickness (LV RWT) was estimated at rest by the formula 2× PWTd/LVEDD (PWTd: diastolic posterior wall thickness; LVEDD: LV end-diastolic diameter). Diagnosis of LV hypertrophy was made in presence of a LVMH higher than 49.2 g/h$^{-2.7}$ in men and 46.7 g/h$^{-2.7}$ in women; hypertrophy was considered eccentric with LV RWT < 0.45 and concentric with LV RWT > 0.45.

In D+ patients, diastolic parameters were evaluated; we measured peak velocities of the early (E) and late (A) transmitral waveforms assessed by pulsed Doppler, with the sample volume placed at the tips of the mitral valve leaflets, their ratio (E/A) and E deceleration time (EDT). We also evaluated E wave propagation rate (EVp) by color Doppler M-mode across the mitral valve, and the ratio of E/EVp, as indicator of LV filling pressure. We also categorized the severity of diastolic dysfunction into the following 4 stages: I (abnormal relaxation) was manifested by an E/A ratio <0.75 and a prolonged DT (>220 ms) with normal filling pressures; II (pseudo normal) was characterized by an E/A ratio between 0.75 and 1.5, short DT (<150 ms), Vp < 45 cm/s or E/Vp < 1.5; III and IV (restrictive pattern), which is reversible or fixed depending on its response to the Valsalva maneuver, had an E/A ratio > 1.5 [18].

Echocardiographic analysis

Echocardiographic images were registered on videotapes during the whole test; at baseline, at the end of low-dose (LD) and HD and after recovery, digital images obtained in parasternal long and short axis and apical four and two chambers view were stored on disk, to allow a quad-screen visualization. LV regional wall motion was assessed according to the recommendations of the American Society of Echocardiography, with a 16 segments model; each segment was given a kinetic score: 0 = not visualized, 1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic and 5 = aneurism. Wall Motion Score Index (WMSI) was calculated at baseline, after LD and HD infusion as ratio between the cumulative sum score and the number of visualized segments.

Inducible ischemia was defined as the development, in at least two segments, of new asynergia or biphasic response (basal asynergia improving at LD and becoming worse at HD); ischemia was considered mild when up to three segments became asynergic during the test and severe for a more extensive involvement.

Follow-up data

Between July and September, 2009 all patients were contacted by telephone to verify the occurrence of new major events (death, both cardiac and non-cardiac, and non-fatal MI). A combined end-point, including cardiovascular death and major cardiovascular event (STEMI, and coronary revascularization) was calculated to evaluate DSE prognostic value in this population.

Statistical analysis

Data were analyzed with SPSS program (SPSS Inc., Chicago, IL, USA). Parametric data were reported as mean ± standard deviation. The comparison between two groups was made with Student test for non-coupled parametric data; the comparison between multiple groups was made with Anova test. Significance was set at $P < 0.05$. Non parametric data were analyzed with Fisher exact test.

Multivariate analysis was performed using a multiple logistic regression model (likelihood ratio method, with variable in by $P < 0.05$, and out $P > 0.10$ to avoid biases due to colinearity) to identify independent predictors of DLVO development.

Results

105 patients in D+ (50%) and 83 in D− group (39%, $P = 0.032$) developed a DLVO, with similar maximum gradient (94 ± 49 mmHg in D+ vs. 86 ± 49 mmHg in D−, P = NS); considering only patients who were not taking beta-blockers (180 in group D+ and 151 D−), D+ subjects reached a higher maximum gradient (56 ± 60 vs. 43 ± 56 mmHg, $P = 0.04$).

Baseline characteristics

Clinical characteristics are shown in Table 1. The two groups were comparable for age and sex distribution; D+ patients showed significantly higher body mass index (BMI) and increased prevalence of other cardiovascular risk factors. Typical or atypical angina was less frequent in D+ subjects that often reported exertional dyspnea. D+ subjects assumed more frequently angiotensin converting enzyme (ACE)-inhibitors (42% in D+ vs. 31% in D−, $P = 0.015$), angiotensin II receptors antagonists (29% in D+ vs. 18% in D−, $P = 0.007$) and dihydropyridines (23% in D+ vs. 13% in D−, $P = 0.006$), while D− patients assumed more frequently verapamil or diltiazem (2% in D+ vs. 10% in D−, $P = 0.001$) and beta-blockers (13% in D+ vs. 28% in D−, $P < 0.0001$); diuretics were equally assumed in the two groups.

Baseline echocardiographic examination (Table 1) showed similar left ventricular ejection fraction (LV EF) in D+ and D− subjects, with significantly increased LV wall thickness and LV mass indexed for height$^{-2.7}$ (LVMH) in D+ patient; an LV eccentric hypertrophy was significantly more frequent among D+ patients (30% in D+ vs. 14% in D−, $P < 0.004$), while concentric hypertrophy had a low and similar prevalence (7% in D+ vs. 4% in D−, P = NS).

DSE parameters

Table 2 summarizes hemodynamic findings during DSE. Peak dobutamine dose was similar in the two groups. D+ patients showed higher cardiac rate all during the test (Fig. 1a) and only atropine

Table 1 Clinical and echocardiographic characteristics in diabetic (D+) and non diabetic (D−) patients

	D+ ($n = 212$)	D− ($n = 212$)	P
Age (years)	66 ± 10	68 ± 11	0.052
Male sex (%)	100 (47)	86 (41)	0.171
BMI (m/kg^2)	29 ± 5	25 ± 3	<0.0001
Hypertension (%)	175 (84)	135 (64)	<0.0001
Dyslipidemia (%)	163 (79)	92 (44)	<0.0001
Smoking habitus (%)	124 (59)	85 (41)	<0.0001
Carotid vascular disease (%)	30 (15)	24 (15)	0.936
Peripheral vascular disease (%)	43 (21)	23 (14)	0.091
Symptoms			
Angina (%)	19 (9)	81 (39)	<0.0001
Effort dyspnoea (%)	49 (23)	24 (11)	0.003
Atypical symptoms (%)	10 (5)	49 (23)	<0.0001
β-blockade therapy (%)	27 (13)	62 (28)	<0.0001
EDD (mm)	50 ± 5	50 ± 6	0.837
ESD (mm)	33 ± 6	35 ± 7	0.058
IVSTd (mm)	9 ± 1	9 ± 2	0.008
IVSTs (mm)	14 ± 2	13 ± 2	<0.0001
PWTd (mm)	9 ± 1	8 ± 1	<0.0001
PWTs (mm)	14 ± 2	13 ± 2	0.002
RWT	0.37 ± 0.1	0.33 ± 0.1	<0.0001
LVMH (g/m$^{-2.7}$)	44 ± 10	39 ± 11	<0.0001
LV EF (%)	58 ± 9	58 ± 11	0.808

EDD end-diastolic diameter, *EDS* end-systolic diameter, *IVSTd* and *IVSTs* diastolic and systolic interventricular septal thickness, *PWTd* and *PWTs* diastolic and systolic posterior wall thickness, *RWT* relative wall thickness, *LVMH* left ventricular mass corrected for height$^{-2.7}$, *LV EF* left ventricular ejection fraction

Table 2 Clinical and hemodynamic data during DSE in diabetic (D+) and non diabetic (D−) patients

	D+ ($n = 212$)	D− ($n = 212$)	P
Peak dobutamine dose (μg/kg/min)	34 ± 7	35 ± 7	0.787
Resting SBP (mmHg)	135 ± 16	135 ± 18	0.999
Peak SBP (mmHg)	153 ± 33	143 ± 31	0.001
Peak DSE EKG mod. (%)	73 (34)	64 (30)	0.406
Peak DSE symptoms (%)	12 (6)	38 (18)	0.0001
Atropine administration (%)	77 (36)	61 (29)	0.097
Ischemia			0.801
No ischemia (%)	146 (69)	145 (68)	
Mild ischemia (%)	22 (10)	26 (12)	
Severe ischemia (%)	44 (21)	41 (19)	

administration determined a similar rate response; to note that all the data about rate response to DSE were analyzed considering only patients not taking beta-blockers.

Among D− patients, reproducibility of symptoms during DSE was higher among patients with DLVO (24 vs. 10%, $P < 0.05$), while among D+ subjects both the prevalence of DSE-evoked symptoms and reproducibility was really very low. The prevalence of DSE-induced EKG modifications was similar in the two groups and an ischemic response, both mild and severe, was evoked in a similar proportion of cases. Among D+ patients, a significantly higher proportion of patients without DLVO concluded the test without any side effect (84 vs. 63%, $P < 0.001$), while in D− the difference was not significantly different (78% vs. 67%, $P = 0.08$); hypotension occurred in a similar proportion of subjects in both groups (D+: no DLVO 3% vs. DLVO 4% $P =$ NS; D−: no DLVO 5% vs. DLVO 4% $P =$ NS). In only 2 patients with DLVO, both in D+ and D− group, the test was prematurely stopped for arrhythmias (1 ventricular and 1 supraventricular in D+ and 2 supraventricular in D−), but a heart rate above 100 b/min has been already reached in all cases and maximum gradient could be evaluated at peak stress.

Clinical and echocardiographic parameters according to DLVO development

We subdivided each group in three subgroups, according to the absence of DLVO, presence of moderate and severe DLVO (Table 3). D− patients with DLVO were significantly younger; to note that, among subjects older than 75 years, ischemia developed much more frequently compared to younger subjects (30/62 vs. 28/150, $P < 0.0001$), probably precluding a DLVO development. No clinical variable was significantly different between subgroups among D+ patients, including diabetes duration (non DLVO: 11 ± 11 years; moderate DLVO 16 ± 11 years; severe DLVO 12 ± 12 years, all $P =$ NS), treatment with insulin (non DLVO: 21%; moderate DLVO 24%; severe DLVO 24%, all $P =$ NS) or metformin (non DLVO: 74%; moderate DLVO 62%; severe DLVO 71%, all $P =$ NS); also degree of metabolic control was similar (HbA1c in subjects without DLVO 8 ± 1%; moderate DLVO 7 ± 1%; severe DLVO 8 ± 1%, all $P =$ NS). Among D− subjects, we did not find any difference in medications assumed by the patients. D+ patients with DLVO assumed more frequently diuretics (25 vs. 11%, $P = 0.01$) and patients on diuretic treatment showed a significant lower LV diastolic volume index (45 ± 6 ml/m^2 vs. 52 ± 14 ml/m^2, $P = 0.002$), while LV EF (59 ± 9 vs. 58 ± 9%, $P =$ NS) and LVMH (47 ± 8 gr/h$^{-2.7}$ vs. 44 ± 11 gr/h$^{-2.7}$, $P =$ NS) were similar.

D+ and D− patients with DLVO, both moderate and severe, showed reduced LV end-diastolic and end-systolic dimension. Diabetic patients with severe DLVO had higher LV EF and lower LVMH compared with diabetic subjects without DLVO; non diabetic patients with moderate or severe DLVO had higher LV EF compared with patients without DLVO. LV hypertrophy was significantly less frequent in D+ patients with DLVO (23 in DLVO+ vs. 42 in DLVO−, $P = 0.029$), while in D− subjects the difference was not significant (8 in DLVO+ vs. 20 in DLVO−, $P =$ NS).

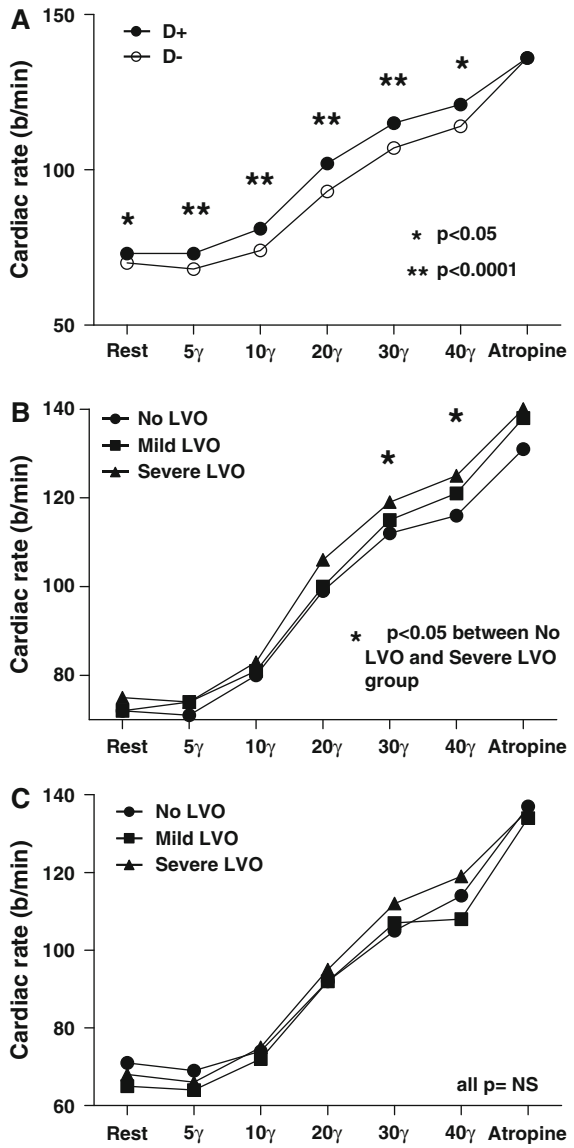

Fig. 1 Heart rate increase during DSE in D+ and D− subjects (**a**); heart rate increase in D+ (**b**) and D− (**c**) patients without DLVO and with moderate and severe DLVO

Among D+ subjects, a higher proportion of patients with DLVO showed normal diastolic function (38% in patients with vs. 22% in patients without DLVO, $P = 0.02$). A type I dysfunction had a similar prevalence in DLVO+ and DLVO− patients (46% of patients with and 49% of patients without DLVO, $P = \text{NS}$), while a type II dysfunction was significantly more common in patients without DLVO (15% of patients with and 29% of patients without DLVO $P = 0.02$); 1 only patients showed type 3 dysfunction. EVp (Table 4), that reflects LV relaxation properties, was significantly higher, and within normal values, in patients with DLVO; subjects with severe DLVO had significantly higher values than patients with moderate DLVO. Ratio of E wave to EVp (E/EVp) was significantly lower in patients with severe DLVO. We also evaluated mitral annular E′ velocity (Table 4), but we were not able to find any significant differences according to presence of DLVO. D+ and D− patients with DLVO showed lower WMSI during all DSE stages and developed less frequently inducible ischemia (Table 3). Peak dobutamine dose was similar in both groups, regardless the presence of DLVO (D−: 34 ± 8 γ/kg/min in DLVO− vs. 36 ± 6 γ/kg/min in DLVO+; D+: 34 ± 8 γ/kg/min in DLVO− vs. 35 ± 7 γ/kg/min in DLVO+, all $P = \text{NS}$); percentage of non diagnostic test was significantly higher only among D− patients in presence of DLVO (40% vs. 19%, $P = 0.002$), while D+ subjects showed a very low and uniformly distributed proportion of non conclusive test (10% in DLVO− vs. 8% in DLVO+, $P = \text{NS}$).

D+ patients with severe DLVO showed a more pronounced heart rate increase during HD dobutamine infusion than D+ patients without DLVO; D− patients' rate increase during DSE was similar despite the presence of DLVO (Fig. 1b, c). DSE determined more frequently chest pain in D− subjects with DLVO, while among D+ patients very few subjects reported symptoms during the test.

Predictors of DLVO development

A multivariate analysis, including age and all echocardiographic parameters that were significantly different between patients with and without DLVO (age, end-diastolic and end systolic diameter, EDD and ESD, LVMH, baseline, LD and HD WMSI, LV EF, and, in D+ patients, treatment with diuretics and EVp), showed that, in D+ patients, the only independent predictor was a smaller EDD (HR 0.779, CI 0.655–0.926, $P = 0.005$); in D− patients lower age (HR 0.878, CI 0.806–0.957, $P = 0.003$), higher LV EF (HR 1.087, CI 1.003–1.177, $P = 0.042$) and lower HD WMSI (HR 0.017, CI 0.001–0.325, $P = 0.007$) were independently associated to presence of DLVO.

Table 3 Clinical and echocardiographic characteristics according to presence or absence of DLVO

	Diabetic subjects ($n = 212$)			Non diabetic subjects ($n = 212$)		
	Non DLVO ($n = 107$)	Moderate DLVO ($n = 24$)	Severe DLVO ($n = 81$)	Non DLVO ($n = 129$)	Moderate DLVO ($n = 25$)	Severe DLVO ($n = 58$)
Age	67 ± 10	68 ± 10	64 ± 9	70 ± 10	64 ± 10*	65 ± 11*
Symptoms						
Angina (%)	13 (12)	2 (8)	4 (5)	47 (37)	8 (33)	26 (45)
Effort dyspnoea (%)	27 (25)	7 (29)	15 (19)	14 (11)	3 (13)	7 (12)
Atypical symptoms (%)	5 (5)	2 (8)	3 (4)	26 (20)	6 (25)	17 (29)
EDD (mm)	52 ± 5	48 ± 5*	47 ± 4*	51 ± 6	48 ± 5	48 ± 4*
ESD (mm)	35 ± 7	30 ± 5*	30 ± 4*	36 ± 8	34 ± 5	32 ± 4*
IVSTd (mm)	9 ± 1	9 ± 1	9 ± 1	9 ± 2	8 ± 1	9 ± 2
PWTd (mm)	9 ± 1	10 ± 1	9 ± 1	8 ± 1	8 ± 1	8 ± 2
RWT	0.35 ± 0.05	40 ± 0.06*	40 ± 0.06*	0.33 ± 0.08	0.32 ± 0.05	0.34 ± 0.08
LVMH ($g/m^{-2.7}$)	46 ± 10	44 ± 9	41 ± 10*	40 ± 11	35 ± 9	37 ± 13
LV EF (%)	55 ± 10	63 ± 7*	64 ± 7*	55 ± 11	65 ± 7*	65 ± 6*
Maximum gradient (mmHg)	4 ± 10	54 ± 10	120 ± 38	4 ± 9	53 ± 9	117 ± 40
DSE-provoked chest pain (%)	5 (5)	1 (4)	6 (7)	15 (12)	7 (28)*	16 (28)*
Rest WMSI	1.20 ± 0.35	1.03 ± 0.09*	1.01 ± 0.08*	1.28 ± 0.41	1.08 ± 0.22*	1.03 ± 0.10*
LD WMSI	1.13 ± 0.26	1.02 ± 0.08*	1.01 ± 0.08*	1.20 ± 0.36	1.02 ± 0.06*	1.01 ± 0.05*
HD WMSI	1.33 ± 0.40	1.09 ± 0.20*	1.04 ± 0.14*	1.38 ± 0.43	1.08 ± 0.16*	1.04 ± 0.13*
DSE induced-ischemia (%)	44 (41)	4 (17)*	7 (9)*	49 (38)	4 (16)*	7 (12)*

* $P < 0.05$ versus non DLVO

EDD end-diastolic diameter, *EDS* end-systolic diameter, *IVSTd* and *IVSTs* diastolic and systolic interventricular septal thickness, *PWTd* and *PWTs* diastolic and systolic posterior wall thickness, *RWT* relative wall thickness, *LVMH* left ventricular mass corrected for height$^{-2.7}$, *LV EF* left ventricular ejection fraction

Table 4 Diastolic parameters according to development of DLVO in diabetic patients

	Non DLVO ($n = 107$)	Moderate DLVO ($n = 24$)	Severe DLVO ($n = 81$)
E wave (m/s)	0.68 ± 0.18*	0.80 ± 0.21	0.72 ± 0.20
A wave (m/s)	0.81 ± 0.15*°	0.94 ± 0.25	0.87 ± 0.16
E/A	0.87 ± 0.25	0.87 ± 0.23	0.84 ± 0.24
DT (m/s)	227 ± 65	211 ± 58	226 ± 64
IVRT (m/s)	94 ± 20	89 ± 14	87 ± 14
EVp (m/s)	0.41 ± 0.08*°	0.46 ± 0.08	0.49 ± 0.10*
E/Vp	1.77 ± 0.35°	1.65 ± 0.27	1.53 ± 0.37
E′ (m/s)	0.11 ± 0.3	0.11 ± 0.3	0.11 ± 0.3
E/E′	7.1 ± 2.8	7.3 ± 2.5	6.8 ± 2.1

* $P < 0.05$ versus Moderate DLVO; ° $P < 0.05$ versus Severe DLVO

DT deceleration time, *IVRT* isovolumin relaxation time, *Vp E* wave propagation velocity; *E′ E′* wave annular velocity

Follow-up

During a median follow-up of 924 ± 134 days, we observed 5 death, in three cases for cardiovascular reason; 8 patients underwent to percutaneous coronary artery revascularization procedures (PTCA, in one case performed in a patient that subsequently died), but nobody referred a new myocardial ischemic event. In patients who developed DLVO we observed only 1 PTCA; all observed deaths were in patients without DLVO, two with inducible ischemia and one in a patient who stopped the test for side effects hypotension (1 events in subjects with DLVO and 10 in subjects without DLVO, $P = 0.0041$). In

patients with DLVO, given the very low number of cardiac events, it was not possible to identify any significant predictive parameter; in subjects without DLVO, age, diabetes length, baseline LV dimension and global systolic function were not different according to cardiac events' occurrence, but peak stress WMSI (1.29 ± 0.37 in patients without vs. 1.71 ± 0.40 in patients with cardiac events, $P = 0.001$) was significantly higher in patients with a worse prognosis.

Discussion

Our study demonstrated that in a population including only patients with suspected CAD, DSE-provoked DLVO had a very high prevalence, especially among diabetic patients. In non-diabetic patients, increasing age independently determined a reduced development of such a response; a preserved systolic function demonstrated the highest predictive power, both expressed as a normal baseline LV EF and a low HD WMSI, that indicates a close to normal segmental kinesis at peak DSE and excludes an extensive ischemic response. In diabetic patients, the main echocardiographic parameter associated with DLVO in diabetic patients was a reduced LV dimension; during follow-up, rate of new major cardiac events was very low, but significantly higher among patients without DLVO.

DSE and DLVO

Development of an hyperdynamic response to dobutamine, with systolic cavity obliteration and intraventricular obstruction, was reported for the first time in the early nineties [19] and occurred in about 20% of patients undergoing DSE; it was initially advocated as a possible mechanism to explain the development of hypotension during the test. Following studies didn't confirm this hypothesis and identified predisposing factors to such a response in female sex, baseline small LV dimensions and normal LV EF [11, 20]; although presence of DLVO reduced DSE sensitivity, especially for single-vessel disease, it showed a favorable long-term prognostic value [10]. Clinical relevance of DLVO remains a topic [21] of debate, for previous conflicting reports [20, 22, 23].

In our study group, DLVO prevalence was higher compared with several previous studies, especially among diabetic patients: differences in DLVO definition and in study entry criteria can in part explain these discrepancies. In this study we excluded patients with ascertained CAD that were included in several previous reports and are less likely to develop DLVO; in fact, previous ischemic episodes frequently determine LV enlargement and baseline wall motion abnormalities, with reduced LV EF, a pattern that often precludes DLVO development. Our results were comparable with two previous studies [12, 13], that included only patients evaluated for chest pain, with angiographically normal coronary arteries. They found a DLVO prevalence similar to what we found, but they were not able to demonstrate any difference in LV dimensions and function between patients with and without DLVO, a discrepancy with our work that could be due to the smaller size of their study populations.

We couldn't confirm previously reported association of DLVO with female sex; we otherwise found that, among non diabetic subjects, DLVO developed less frequently in the elderly: this data was probably due to a significantly higher prevalence of inducible ischemia in old subjects. We didn't observe any association between DLVO and hypotension during DSE, both among diabetic and non-diabetic patients.

Among D− subjects, patients who developed DLVO frequently experienced chest pain during DSE, in agreement with previous report: given the very low prevalence of an ischemic response among these subjects, this symptom could be due to a microvascular angina determined by the very high work load imposed to the LV by DLVO. The very high prevalence of arterial hypertension and dyslipidemia observed in our study population could also facilitate such a response.

Diabetes and DLVO

In our study group, DLVO prevalence was disproportionably high among diabetic patients: this is a new finding because data about prevalence of diabetes in patients with or without DLVO were not reported in several previous studies or there were not significant differences; only Secknus et al. [10] reported a significant minor prevalence of DLVO in diabetic patients.

Our results are otherwise in agreement with the study of Coisne et al. [16] who examined by DSE 49 diabetic patients with suspected CAD and found a DLVO prevalence of 59%, significantly higher respect to the prevalence of 22% observed in non-diabetic patients included as control group. They could not demonstrate significant differences in LV geometry between patients with and without DLVO, both diabetic or not; in agreement with our results, heart rate in diabetic patients was higher respect to the control group before and at the end of the test.

In our study population in D+ subjects, the LV geometry associated with a higher prevalence of DLVO was characterized by smaller end-systolic and end-diastolic dimension, lower mass index and higher RWT: this pattern represents a truly "normal" LV geometry, on which the positive inotropic effect of dobutamine can fully exert its effect, determining a marked increase in contractility. On the other hand, prevalence of LV hypertrophy was significantly lower in patients who developed DLVO. Development of hypertrophy, in response of a chronic pressure overload probably represented in these patients by arterial hypertension, is characterized by myocyte growth, since the proliferative capacity of cardiac myocytes is absent or at best very limited [24]; this process is associated with activation of a molecular program that determines an altered intracellular calcium handling, increased rate of apoptosis and enhanced extracellular matrix deposition leading to reduced myocardial relaxation. All these modifications interfere with myocardial contractility and probably prevent the marked hypercontractility required to develop DLVO. Moreover LV hypertrophy was found to be associated with increased morbidity and mortality, that we did not find in this population, especially in patients with DLVO.

Diastolic function was significantly better in patients with DLVO, both considering single parameters and prevalence of categorized diastolic dysfunction. We found a discrepancy between different diastolic parameters, as according to Vp values the difference was significant while according to E/E′ it was not. Although both Vp and E′ reflect LV relaxation property, this discrepancy could be due to the fact that in normal heart Vp is more preload-independent than mitral annular velocity [18] and can accurately evaluate the presence or absence of an abnormal relaxation. Given the higher prevalence of treatment with diuretics among D+ patients with DLVO, the associated decrease in preload could determine a false reduction of E′ and a concomitant increase in E/E′ in patients with DLVO. E/E′, whose mean value was normal in all groups, could therefore be slightly increased in patients without DLVO for relaxation abnormalities and in patients with DLVO for decreased preload.

LV segmental wall motion was better all during the test and an ischemic response developed in a very limited proportion of patients. Heart rate was higher in diabetic respect to non-diabetic patients both baseline and all during the test; diabetic patients who developed DLVO showed higher heart rate at HD infusion respect to diabetic patients without DLVO.

Development of DLVO during DSE in diabetic patients seems therefore a result of several mechanisms that variably combine to bring such a response: a normal heart, considering both systolic and diastolic dimensions and function, a relative hypovolemia induced by diuretic treatment and an increased heart rate at rest and during stress.

The presence of a significantly higher heart rate, both at rest and during the test, could be an early sign of parasympathetic dysfunction, leaving an unbalanced prevalence of sympathetic drive of cardiac rate and contractility. In fact, although diabetic autonomic neuropathy (DAN) [25, 26] is a system-wide disorders, affecting all parts of the autonomic nervous system, it manifests first in longer nerves, such as vagus nerve, which is the longest of such system and is responsible of cardiac parasympathetic innervation. It is possible that, in presence of a narrow ventricle, dobutamine induced a disproportionally high increase in contractility, resulting in cavity obliteration and DLVO development. Other indirect signs associated with DAN, like diabetes' duration and peripheral neuropathy, were not different between patients with and without DLVO, but this response could be an early feature of this diabetic complication.

Prognostic value of DLVO

Beyond DLVO pathogenesis, in this diabetic population evaluated with DSE for CAD screening we confirmed the positive prognostic value of DLVO development: cardiac events during follow-up were few, but all except one restricted to patients without

DLVO. It doesn't seem like that we lost a diagnosis of CAD in a significant proportion of patients due to DLVO development as we know that CAD in diabetic subjects portends a bad prognosis. This follow-up results allow us to say that these patients, with normal baseline LV geometry and function and DLVO during DSE, represent a very low risk population. We choose to define DSE-induced DLVO as a maximum gradient of at least 36 mmHg, the highest value reported in previous work [12, 16, 20]: we can argue that to develop at least that gradient, or higher, a normal global and segmental LV systolic function is required and it is very unlikely the underlying existence of a CAD, also in case of monovasal involvement. A careful management of coexisting cardiovascular risk factors remains mandatory for its proved prognostic advantage [27], but further tests to evaluate CAD existence don't seem to yield significant benefits.

The main limitations of this study are the retrospective design and the lack of coronary angiographic data, to confirm DSE results; follow-up results can in part overcome this limitation because, beyond presence of anatomical coronary lesions, we were able to ascertain the very low prevalence of cardiac events in patients with DLVO. We also had not any data about heart rate variability that could support our conclusion: however, this is a possible future area of investigation, to better clarify the inotropic effect of dobutamine according to LV geometry and the role of dobutamine stress echocardiography in CAD screening in diabetic patients.

Conflict of interest None.

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