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Influence of preload and afterload on stroke volume response to low-dose dobutamine stress in patients with non-ischemic heart failure: A cardiac MR study

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ABSTRACT

Background: Lack of increase in left ventricular (LV) stroke volume (SV) during low-dose dobutamine stress (LDD) is attributed to exhausted cardiac contractile reserve in failing heart. However, the role of the afterload and preload in SV changes is underestimated. The aim of the study was to investigate the effects of LDD on preload reserve and afterload in patients with non-ischemic heart failure.
Methods: 58 patients (age 62 years) underwent LDD (up to 20 μg/kg/min) using cardiac magnetic resonance.
Results: LV-SV increased by 27% in 24 patients ($p<0.001$) (SV+), while decreased by 19% in 22 patients ($p<0.001$) (SV−). The LDD-to-rest reduction in preload, as defined by LV end-diastolic volume (EDV), was more pronounced in SV− than SV+ (24% and 8% respectively, $p<0.05$). The LLD-to-rest increase in systolic blood pressure to LV end systolic volume ratio, an index of LV contractility, was higher but not statistically different in SV+ in comparison to SV− (70% vs 48%, p = ns). Systemic vascular resistance during LDD tended to be higher in SV− (23%, p = ns), while it was significantly reduced in SV+ (9.5%, $p<0.011$), whereas arterial elastance (Ea) increased in SV− (30%, $p<0.001$) but decreased in SV+ (0.5%, $p=0.04$). At multivariable regression models LV-EF, LV-EDV and Ea significantly contributed to LV-SV changes in all patients. Also among SV+ and SV− LV-EDV and Ea revealed significant contribution to LV-SV change.
Conclusions: At similar contractile reserve response, the lack of LDD-induced increase in LV-SV, can be related to reduced preload reserve as well as to increased afterload.

1. Introduction

The low-dose dobutamine stress (LDD) is widely used in the diagnostic and/or prognostic setting of patients with cardiac diseases [1–4]. In patients with dilated cardiomyopathy (DC), the LDD test combined to non-invasive cardiac imaging is widely used to assess the contractile reserve of dysfunctional myocardium [5–8]. Magnetic Resonance Imaging (MRI) is an accurate diagnostic tool to investigate non-invasively both preload and contractile function at rest and during stress [9,10]. The assessment of LDD responsiveness is clinically relevant to identify patients with preserved cardiac performance and better prognosis in the presence of chronic heart failure (HF) [11,12]. The increase of stroke volume (SV), ejection fraction (EF) and cardiac output (CO) as well as the decrease of the end-systolic volume (ESV) during LDD stress defines the pattern of contractile reserve [13]. The lack of increase of left ventricular (LV) SV and EF during LDD is an independent prognostic marker of functional impairment of the heart in patients with non-ischemic DC [14,15]. However, the changes of LV-EF and SV do not always reflect the proper state of myocardial function and cardiac performance of patients with heart failure [16,17]. In fact, these parameters of global cardiac function are influenced by several factors beyond contractility per se, including loading conditions and chamber geometry. In the presence of unchanged afterload, the preload recruitment during inotropic stimulus can increase LV force development maintaining the stroke volume at physiological level in accord with the Frank–Starling mechanism, which is still preserved in human end stage failing myocardium [18]. Moreover, the positive lusitropic effect of inotropic agents, as dobutamine, contributes to reduce the LV end-diastolic wall stress and improve LV early refilling by increasing cardiac performance of failing heart in a preload-dependent manner [19]. A recent study reveals that DC patients with increased LV end-diastolic volume and stroke volume during exercise stress test have better prognosis [20].

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To highlight the clinical relevance of preload responsiveness during physiological stress, additional studies are sorely needed. The aim of our study was to assess the impact of changes in preload reserve and afterload on the magnitude of SV response during LDD in patients with non-ischemic DC.

2. Methods

2.1. Patients

Forty six consecutive patients (mean age 62 ± 12 years, 44 males) with stable chronic non-ischemic DC were referred to the magnetic resonance (MR) laboratory to perform LDD stress test in order to assess contractile reserve. Patients with non-ischemic DC diagnosed on the basis of echocardiographically documented end-diastolic diameter >56 mm, LV-EF <50% and normal coronary angiography, entered the study. Exclusion criteria were: 1) history of life-threatening ventricular arrhythmias, 2) absence of sinus rhythm, 3) absolute contraindication to MR and 4) unstable clinical conditions. In addiction twelve subjects with EF >55% of left ventricle, atypical chest pain and without history or documentation of heart disease served as the control group. These subjects were referred to the MR to perform high-dose dobutamine stress test in order to exclude the presence of inducible myocardial ischemia. From this group, data obtained at LDD only, were used for comparison with DC patients. According to the increase or decrease of LV-SV during LDD, patients with LV dysfunction were clustered into two groups: SV+ patients (n=24) increasing SV during LDD, as opposed to SV− patients (n=22) decreasing SV during LDD.

All patients and controls gave their written informed consent. The study was approved by the local ethics review committee, and the investigation conformed with the principles outlined in the Declaration of Helsinki (Br Med J 1964;ii:177).

2.2. Low dose dobutamine stress testing

Dobutamine was infused in 5-min dose increments, starting from 5 μg/kg/min and increased to 10 and 20 μg/kg/min, each step lasting 5 min. Systolic (S), diastolic (D) and mean (M) arterial pressure (AP) and heart rate (HR) were measured at rest and during LDD stress. The test was interrupted for one of the following reasons: intolerable symptoms, limiting asymptomatic side effects, consisting of a) hypertension (SAP >200 mm Hg; DAP >110 mm Hg); b) hypotension (relative or absolute): >30 mm Hg fall in AP; c) supraventricular arrhythmias; d) ventricular arrhythmias. All the cardiovascular parameters were measured in basal condition and during LDD at peak dose of dobutamine in both control and DC groups.

2.3. Cardiac magnetic resonance data acquisition

Cardiac MR was performed using a dedicated 1.5 T whole body scanner (Hdx, GE, Milwaukee, Michigan, USA) with a Cardiac Phased Array 8 channel coil. MR included evaluation of left and right ventricular function at rest and LDD. A breath-hold segmented-gradient echo fast imaging employing steady-state acquisition (FIESTA) ECG-triggered sequence was used to evaluate left and right ventricular function by using standard parameters. In each patient a total of 9 to 12 short-axis views (depending on the LV volume) and 2 long-axis views (one vertical and one horizontal) were acquired, with a minimum of 30 cine frames for each slice [21,22]. Delayed enhancement was obtained in order to assess the presence of myocardial fibrosis. A fast gradient echo inversion recovery sequence was utilized. Delayed enhancement images were recorded 8–10 min after bolus injection of gadobutrol (Gadovist®, Schering, Germany; 0.2 mmol/kg); images were acquired in the same short axis and long axis slices as used for cine MR [23]. A free breathing phase-velocity cine MR technique (PVC MR) was used for determination of regurgitant stroke volume of both ventricles in order to assess mitral and tricuspid regurgitation [24,25]. Briefly, the through-plane flow was measured orthogonal to the vessels in the ascending aorta and in the pulmonary artery by an acquisition plane placed 5 mm over valvular plane. The following acquisition parameters were used: TR/TE 12/5 ms, flip angle 20°, field of view 30, phase field of view 1, matrix 192×192, reconstruction matrix 256×256, slice thickness 5 mm, and number of excitation 5. Flow sensitivity was set to 250 cm/s of encoded velocity and raised if aliasing artifact occurred. The number of cardiac phases was set according to the heart rate, in order to obtain a temporal resolution of aortic wall excursion of approximately 10^{-3} s.

2.4. Cardiac magnetic resonance measurements

The FIESTA and PVC MR imaging sequences for the assessment of ventricular function, flows and wall excursion, pulmonary and aortic flow were transferred to a workstation (Advantage Windows 4.1 GE) and elaborated by means of a commercially available software (Mass plus and CV Flow respectively, MR Analytical Software Systems, version 4.0, Leiden, The Netherlands). Briefly, endocardial and epicardial contours were automatically traced in all the cine short axis images of all temporal phases. Manual correction of contours was performed when appropriate. The volumetric data of left and right ventricles were plotted against the time (in ms) in a volumetric time curve (Figs. 1 and 2) for left ventricle only. From these curves the end-diastolic

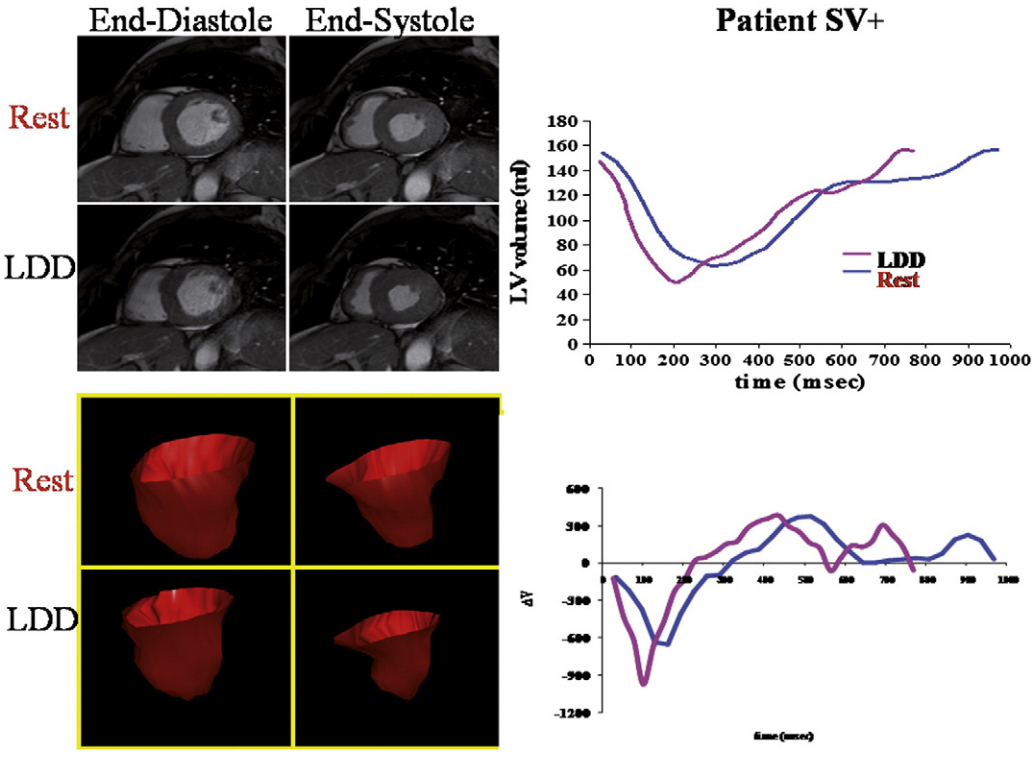

Fig. 1. Evaluation of LV volumes in a patient SV+ at rest and during LDD stress. Left upper panel: end-diastolic and end-systolic frames of a SSFP basal short axis view at baseline (rest) and during infusion of dobutamine at peak dose (LDD); left lower panel: three-dimensional reconstruction of the LV chamber in end-diastole and end-systole at rest and during LDD at peak dose; right upper panel: representative LV volume/time curve at rest (blue) and during LDD stress (red) showing a minimal decrease in LV volumes at peak dose of dobutamine; right lower panel: representative dV/dt curve of LV at rest and during LDD stress at peak dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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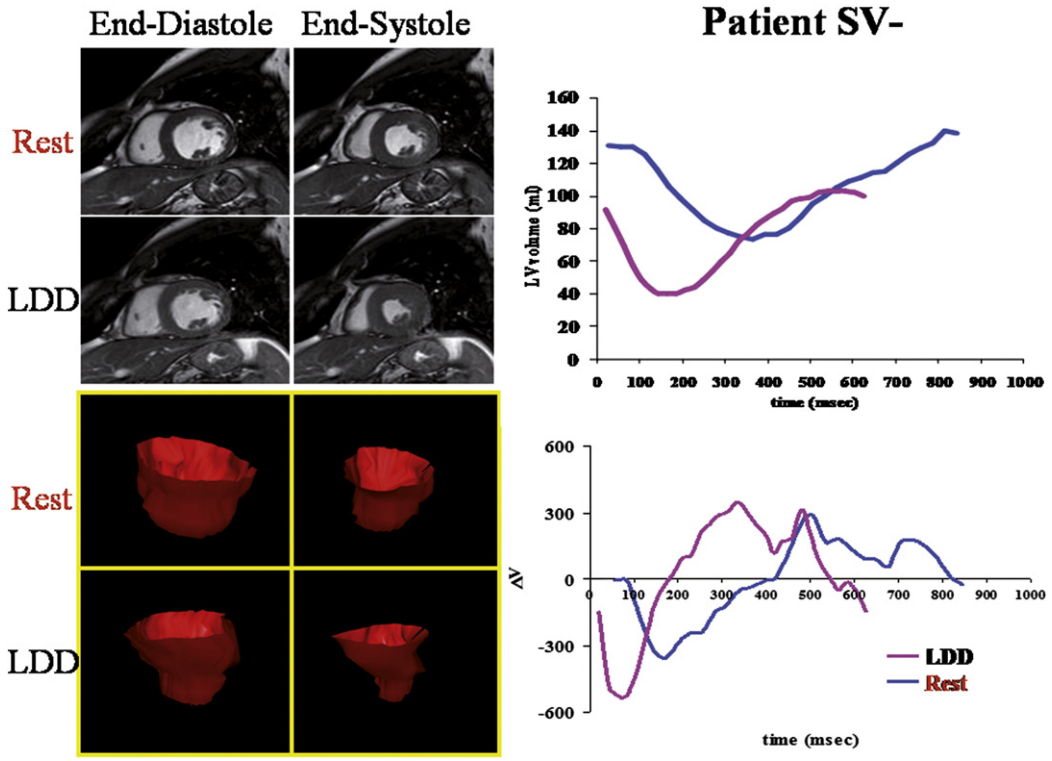

Fig. 2. Evaluation of LV volumes in a patient SV− at rest and during LDD stress. Left upper panel: end-diastolic and end-systolic frames of a SSFP basal short axis view at baseline (rest) and during infusion of dobutamine at peak dose (LDD); left lower panel: three-dimensional reconstruction of the LV chamber in end-diastole and end-systole at rest and during LDD at peak dose; right upper panel: representative LV volume/time curve at rest (blue) and during LDD stress (red) showing a marked reduction in LV volumes at peak dose of dobutamine; right lower panel: representative dV/dt curve of LV at rest and during LDD stress at peak dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(EDV, ml) and end-systolic volumes (ESV, ml) were measured and EF (%) and SV (ml) of both ventricles were derived. Cardiac output (CO, ml bpm) was calculated as the product between the SV and HR. The ratio between SAP and LV-ESV (SAP/LV-ESV) was calculated as a global contractility index of left ventricle [26]. Systemic vascular resistance (SVR, mm Hg/min/l) was calculated as the ratio of mean arterial pressure to cardiac output [27]. Arterial Elastance (Ea, mm Hg/ml) was calculated as follows: (SBP × 0.9)/SV [28]. End-diastole corresponded to peak of electrocardiographic R wave while end-systole corresponded to the smallest LV cavity during the cardiac cycle.

Diastolic parameters of the left ventricle were calculated from the time derivative of LV volume (LV dV/dt) curve as previously described [29,30]. Briefly, a LV dV/dt curve was generated as the first derivative transformation of the volumetric time curve. The early (E) and late (A) peak filling rate (PFR) and the E/A ratio were measured as, respectively, the early and the late diastolic peak of LV dV/dt curve (Fig. 1).

The extent of delayed enhancement was measured as previously described [22,23]. Enhanced myocardium was defined as myocardium with a signal intensity of ≥2 standard deviations above the mean of the region of interest. The LDD to resting differences of the variables were calculated as follows: (LDD-resting)/resting 100.

Mitral and tricuspid regurgitation were assessed by subtracting the forward flow of the great vessel (aortic and pulmonary forward flow for the quantification of mitral and tricuspid valve regurgitation), calculated by PVC MR, from the stroke volume (volumetric computation) of the corresponding ventricles (left and right ventricles for mitral and tricuspid valve regurgitation, respectively). Normalizing the regurgitation volume to the corresponding ventricular stroke volume, the regurgitation fraction was calculated.

2.5. Plasma assays

The plasma level of amino-terminal pro-brain natriuretic peptide (NT-proBNP), was measured with an automated electrochemi-luminescent immunoassay as previously described [31]. Creatinine was measured in a timed plasmatic sample.

2.6. Statistical analysis

All data were analyzed using SPSS software (version 13). Categorical variables are presented as number of subjects (percentages) and continuous variables are expressed as means ± 1 SD or median (25th–75th percentile) where appropriate.

Fisher and χ^2 test were used to compare categorical variables. Independent *T* test and Mann–Whitney *U* test were used to compare parameters between controls and all DC patients. One-way analysis of variance (ANOVA) and Kruskal–Wallis test were used to compare data between the three groups and post hoc comparisons were performed respectively using Bonferroni post hoc tests or Mann–Whitney *U* test with Bonferroni correction for p-value. Paired *T*-test and Wilcoxon test were used to compare parameters after and before LDD within groups. Univariable linear regression analysis was used to identify variables contributing to SV change in all patients as well as within groups of resting variables and their LDD-induced change. The relative contribution of resting variables and their LDD-induced change was then evaluated using multivariable regression models. Resting variables as well as induced changes were entered into univariable regression analysis; then, all variables whose significance level was <0.1 were entered into the multivariable model. Stepwise methods as well as clinical considerations were used to build up the final model. A p-value<0.05 was considered to be statistically significant.

3. Results

3.1. Controls vs DC patients. Clinical characteristics

Clinical, hemodynamics and resting LV and RV parameters of controls, SV− and SV+ DC patients are shown in Table 1. Compared to controls, DC patients showed significantly larger LV EDV and ESV, lower LV-EF, and SAP/LV-ESV. Conversely, EDV and ESV of right ventricle were similar to controls. Clinical and bio-humoral parameters between SV+ and SV− were similar with the exception of higher number of subjects with dyslipidemia in SV−. With regard to cardiac MR parameters, SV− showed higher LV-SV, higher DT, PFR-A and E/A ratio, but lower Ea in comparison to SV+. No DC patient showed intramyocardial enhanced areas.

3.2. Baseline to LDD changes in cardiac MR parameter

LDD testing was completed in all patients without any inconvenience or side effects. All the controls had a maximal negative high dose dobutamine stress test for myocardial ischemia. LDD-induced changes are reported in Table 2 and the LDD to rest differences are reported in Table 3. Figs. 1 and 2 show two representative examples

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Table 1
Clinical characteristics, hemodynamics, left and right ventricular parameters at rest.

Variables	Controls (n = 12)	DC (n = 46)		
		All DC	SV+ (n = 24)	SV− (n = 22)
Rest				
Male	9(75%)	35(76%)	20(83%)	15(68%)
Age	55 ± 10*	64 ± 12†	63 ± 14	65 ± 9‡
Hypertension	5(42%)	27(59%)	11(46%)	16(73%)
Diabetes	1(8%)	9(20%)	4(17%)	5(23%)
Dyslipidemia	3(25%)	19(41%)†	6(25%)	13(59%)§
Smoke	3(25%)	21(46%)	9(38%)	12(55%)
LBBB	2(17%)	17(37%)	10(42%)	7(32%)
NYHA Class >1	0	27(60%)	13(57%)	14(64%)
Hb (g/dl)	14 ± 0.7	14 ± 1.3	14 ± 1.3	13 ± 1.2
Creatinine (mg/dl)	0.9 ± 0.1*	1.1 ± 0.3†	1.2 ± 0.4‖	1 ± 0.3
NT-proBNP (ng/l)	–	944 (424–1963)	844 (193–2494)	982 (724–1875)
PCR (mg/dl)	0.09 (0.08–0.1)*	0.4(0.1–0.8)†	0.3(0.2–0.6)‖	0.67(0.1–1.3)
HR (bpm)	66 ± 9	70 ± 11	70 ± 13	70 ± 8
SAP (mm Hg)	140 ± 13	134 ± 18	130 ± 15	138 ± 20
DAP (mm Hg)	84 ± 9	80 ± 11	79 ± 10	81 ± 13
MAP (mm Hg)	103 ± 8	97 ± 12	96 ± 10	99 ± 13
Left ventricle				
EF (%)	64 ± 8*	33 ± 10†	30 ± 10‖	35 ± 9‡
EDV (ml)	111 ± 34*	228 ± 77†	216 ± 88‖	241 ± 63‡
ESV (ml)	41 ± 19*	157 ± 70†	154 ± 81‖	159 ± 58‡
SV (ml)	70 ± 18	71 ± 24†	62 ± 23	82 ± 21§
PFR E(ml/s)	308 ± 111*	213 ± 70†	202 ± 85‖	226 ± 49‡
PFR A (ml/s)	251 ± 71	255 ± 99†	193 ± 82	322 ± 67‡, §
DT (mm/s)	188 ± 45	165 ± 54†	142 ± 53‖	190 ± 45§
E/A	1.3(0.8–1.8)	1.3(0.8–1.2)†	1.2(1.0–1.5)	0.9(0.8–0.9)§
SVR (mm Hg/min/l)	23(19–29)	28(21–34)	31(23–35)	25(21–30)
CO (l/min)	5 ± 1	4 ± 1†	3 ± 1‖	4 ± 2
SAP/ESV	4 ± 2*	1 ± 0.5†	1 ± 0.5‖	1 ± 0.4‡
Ea (mm Hg/ml)	1.9 ± 0.7	1.9 ± 0.9†	2.3 ± 1	1.6 ± 0.4§
Right ventricle				
EF (%)	56 ± 8	60 ± 13	57 ± 12	64 ± 14
EDV (ml)	104 ± 40	119 ± 38	111 ± 36	129 ± 38
ESV (ml)	46 ± 21	48 ± 24	48 ± 19	48 ± 29
SV (ml)	59 ± 22	69 ± 28	62 ± 29	76 ± 25

LBBB = left bundle branch block, Hb = hemoglobin, NT-proBNP = n-terminal pro brain natriuretic peptide, PCR = protein C reactive, HR = heart rate, DAP = diastolic arterial pressure; SAP = systolic arterial pressure, MAP = mean arterial pressure, EF = ejection fraction, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, PFR = peak filling rate; DT = deceleration time, SVR = systemic vascular resistance, CO = cardiac output, SAP/ESV = systolic arterial pressure/end-systolic volume ratio, Ea = elastance.

* $p<0.05$ for comparison between controls and DC, independent *T*-test or Mann–Whitney *U* test appropriately.

† $p<0.05$ for comparison between controls, SV+, SV−, ANOVA or Kruskal–Wallis test appropriately.

‖ $p<0.05$ for post-hoc comparison between controls and SV+.

‡ $p<0.05$ for post-hoc comparison between controls and SV−.

§ $p<0.05$ for post-hoc comparison between SV+ and SV−.

Table 2
Hemodynamics, left and right ventricular parameters during LDD.

Variables	Controls (n = 12)	DC (n = 46)		
		All DC	SV+ (n = 24)	SV− (n = 22)
Dobutamine				
HR (bpm)	92 ± 19*	94 ± 22*	92 ± 21*	97 ± 24*
SAP (mm Hg)	143 ± 20	150 ± 20*	150 ± 21*	150 ± 21*
DAP (mm Hg)	78 ± 13	76 ± 13	78 ± 12	74 ± 13*
MAP (mm Hg)	100 ± 14	100 ± 12	102 ± 12	99 ± 13
Left ventricle				
EF (%)	81 ± 9*	41 ± 15*	42 ± 17*	39 ± 12*
EDV (ml)	100 ± 38*	191 ± 76*	199 ± 91*	182 ± 58*
ESV (ml)	21 ± 15*	119 ± 69*	123 ± 83*	115 ± 50*
SV (ml)	78 ± 26	71 ± 24	76 ± 25*	67 ± 22*
PFR E (ml/s)	387 ± 168	256 ± 91*	299 ± 87*	209 ± 71
PFR A (ml/s)	307 ± 72	231 ± 105	262 ± 131*	197 ± 52*
DT (mm/s)	165 ± 76	120 ± 27*	119 ± 30	122 ± 24*
E/A	1.2(0.8–1.8)	1.4(1.1–1.6)*	1.3(1.1–1.6)	1.4(1.3–1.8)*
SVR (mm Hg/min/l)	21(20–25)	26(22–35)	25(20–34)*	29(23–37)
CO (l/min)	7 ± 1.5*	5 ± 2*	6 ± 2*	5 ± 2
SAP/ESV	10 ± 7*	1.8 ± 1.1*	1.9 ± 1.3*	1.7 ± 1*
Ea (mm Hg/ml)	1.8 ± 0.5	2.1 ± 0.6	2 ± 0.7	2.2 ± 0.6*
Right ventricle				
EF (%)	69 ± 8*	63 ± 10*	60 ± 11	66 ± 8
EDV (ml)	89 ± 30	86 ± 23*	93 ± 23*	79 ± 21*
ESV (ml)	28 ± 16*	35 ± 14*	40 ± 14*	30 ± 11*
SV (ml)	62 ± 19	53 ± 17*	53 ± 20	54 ± 14*

Abbreviations: see Table 1.

* $p<0.05$ for comparison between LDD and rest values, paired *T*-test or Wilcoxon test appropriately.

of changes in LV volumes during the cardiac cycle in SV+ and SV− DC patients. The decrease of LV-EDV was significant among DC patients and was more pronounced in SV− than the SV+ group. Conversely, CO was unchanged in SV− while increased in controls and SV+. The increase of the LV-EF was significant in all patients and less marked in SV− than in the other two groups. The LDD-to-rest increase in SAP/LV-ESV was similar in SV− and SV+, reaching values still much lower than in controls. Otherwise, SVR during LDD was unchanged compared to baseline in SV− patients, but they were significantly reduced in control and SV+ patients whereas Ea increased in SV− and reduced significantly in SV−.

Regarding RV, RV-EDV reduced significantly in SV+ and SV−, whereas RV-SV remained unchanged in SV+ and reduced in SV−.

Changes in diastolic parameters were specular between SV− and SV+: A and E waves PFR decreased in SV− patients while increased in SV+. There was no statistical difference in mitral and tricuspid regurgitation between SV+ and SV− at rest and during LDD. Furthermore, rest to LLD changes in mitral and tricuspid regurgitation were not significantly different in SV+ and SV− (mitral regurgitation: SV+ rest 20 ± 8%, LDD 17 ± 12%; SV− 21 ± 9%, LDD 20 ± 10%; tricuspid regurgitation: SV+ rest 5 ± 5%, LDD 5 ± 2.5%; SV− 4 ± 2%, 42.6.%).

3.3. Regression analysis

Results of univariable and multivariable regression models are shown in Table 4 and, in which the significant coefficients are reported. At multivariable analysis the increase of LV-EF and LV-EDV determined a rise in LV-SV while a decrease in Ea contributed to increase LV-SV. Similarly when SV− and SV+ patients were considered, the 2 independent variables were LV-EDV and Ea.

3.4. Plasma assays

NT-proBNP values were similar in DC patients (944 ng/l). Similarly, creatinine was increased in DC patients compared to controls (1.11 ± 0.33 vs 0.89 ± 0.07 mg/dl, $p<0.022$) despite similar hematocrit values.

4. Discussion

Our study showed that the lack of stroke volume increase in response to LDD depends on a reduction of preload reserve and increase in afterload in the presence of blunted contractile reserve in patients with non-ischemic DC. Among patients with non-ischemic DC and similar LV-EF, LDD did not increase LV-SV in 38% of patients.

As expected, LDD enhanced global LV function in control patients in accord with an increased contractility (increased SAP/LV-ESV ratio) and reduced SVR. Moreover, the left and right ventricular

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Table 3
LDD-to rest differences in hemodynamics, left and right ventricular parameters.

Variables	Controls (n = 12)	SV+ (n = 24)	SV− (n = 22)	p-Value			
				Overall	Controls	SV+	SV−
Δ% HR	38.2 ± 23.1	34.6 ± 32.8	39 ± 30.7	<0.001	<0.001	<0.001	<0.001
Δ% SAP	2.4 ± 16.6	16 ± 18.2	9.3 ± 15.5	<0.001	ns	<0.001	0.011
Δ% DAP	−7.7 ± 11.9	0.3 ± 20.9	−7.2 ± 18.1	0.024	ns	ns	0.039
Δ% MAP	−2.6 ± 12.6	7.5 ± 17.7	0.8 ± 16.2	ns	ns	ns	ns
Left ventricle							
Δ% EF	26.3 ± 14	37.1 ± 27.4	9.8 ± 15.8	<0.001	<0.001	<0.001	0.023
Δ% EDV	−10.8 ± 13.4	−7.9 ± 18.4	−24.4 ± 18.1	<0.001	0.014	0.048	<0.001
Δ% ESV	−51.8 ± 21.1	−23.9 ± 24.7	−26.4 ± 26.3	<0.001	<0.001	<0.001	<0.001
Δ% SV	11.2 ± 20.3	26.7 ± 25.3	−19.3 ± 14	ns	ns	<0.001	<0.001
Δ% PFR E	11(−13.2 to −40.3)	56.7(50.6–68.5)	−10.5(−16.2 to −2)	<0.001	ns	<0.001	0.046
Δ% PFR A	15.3(−6.6–50.1)	35.8(7.1–57)	−37.5(−43.2 to −34.2)	ns	ns	0.023	<0.001
Δ% DT	−25.1(−36.5–9.3)	−13.7(−34.6 to −2.2)	−39.5(−42 to −31.5)	<0.001	ns	ns	<0.001
Δ% E/A	−18.1(−22.6–61.6)	8.7(−13.8–35)	62.8(39.7–116.7)	0.008	ns	ns	<0.001
Δ% SVR	−0.7(−30.4–17.1)	−9.5(−30.8–8.6)	22.7(−23.2–57.8)	ns	ns	0.011	ns
Δ% CO	53.6 ± 42.6	67.4 ± 42	9.6 ± 23.2	<0.001	0.001	<0.001	ns
Δ% SAP/ESV	117.8(62.9–174.2)	69.2(19.8–101.9)	47.6(21.7–98)	<0.001	0.002	<0.001	0.031
Δ% Ea	−6.2(−20.0–7.7)	−0.5(−22.5–7.9)	29.9(17.6–69.0)	ns	ns	0.037	<0.001
Right ventricle							
Δ% EF	−8.6(−29.8–8.5)	−14.2(−29.4–9.8)	−42.1(−44.9 to −27.7)	<0.001	0.003	0.037	ns
Δ% EDV	−12.1 ± 20.1	−11.6 ± 21.7	−37 ± 12.4	<0.001	ns	0.007	<0.001
Δ% ESV	−36.8 ± 22.2	−7 ± 37.1	−30.4 ± 21.8	<0.001	0.001	0.038	0.001
Δ% SV	44.3(17–51)	45.2(19.1–74.8)	46.3(22.4–83.7)	0.002	ns	ns	0.001

Abbreviations: see Table 1.

preloads, as defined by respective EDV, slightly decreased and diastolic function improved, according to enhanced early and late PFR.

In SV− patients the EDV of both ventricles was markedly reduced during LDD compared to SV+ and control patients in the presence of increased afterload, as shown by the increase in Ea, and in the presence of inotropic reserve that was blunted in comparison to control, although it was similar to SV+. The increase of heart rate guaranteed only the preservation of CO and EF during LDD stress in the presence of unfavorable changes in cardiac loading conditions. Importantly there were no significant changes in mitral or tricuspid regurgitation.

Using the pressure/volume framework for the analysis of the interaction between cardiac loading changes and function, at rest relative to control SV+ and SV− have lower systolic function as indicated by the lower slope of the systolic pressure/end diastolic volume (Fig. 3, dashed thin lines) and higher ventricular volumes. Higher end-diastolic volumes (preload) in SV+ and SV− are associated with stroke volume values (Fig. 3, numbers and horizontal bars) similar to controls. The compensatory utilization of preload reserve is particularly evident in SV− group. LDD increases inotropism in controls as well as in patients with DC, according to the increase in slope of the thin dashed lines (Fig. 3, arrows). However, the larger decrease in preload in SV− as compared to the other groups and the increased arterial elastance (approximated by the pressure/volume slope during ejection) are responsible for the drastic reduction in stroke volume. Thus, decrease in stroke volume during the test may not be expression of more depressed

Table 4
Univariable and multivariable regression analyses of LDD-induced changes in LVSV.

Univariable models*	All patients (n = 58) (n = 12)		SV+ (n = 24)		SV− (n = 22)	
	β (CI 95%)	p-Value	β (CI 95%)	p-Value	β (CI 95%)	p-Value
Rest LVSV (ml)	−0.55(−0.86 to −0.25)	0.001	−0.52(−0.95 to −0.10)	0.019		
Rest PFR A (ml/s)	−0.12(−0.20 to −0.04)	0.003				
Rest DT (mm/s)	−0.20(−0.34 to −0.07)	0.004				
Rest CO (l/min)	−6.44(−12.30 to −0.58)	0.032				
Δ% DAP	0.45(0.05–0.86)	0.030				
Δ% MAP	0.49(0.04–0.94)	0.035				
Δ% EF	0.67(0.40–0.94)	<0.001				
Δ% EDV	1.07(0.77–1.37)	<0.001	0.87(0.40–1.34)	0.001	0.50(0.23–0.77)	0.001
Δ% ESV					0.23(0.01–0.46)	0.043
Δ% PFR E	0.21(0.08–0.34)	0.003				
Δ% PFR A	0.06(0.01–0.12)	0.025				
Δ% E/A	−0.10(−0.18 to −0.02)	0.021				
Δ% SVR	−0.27(−0.44 to −0.09)	0.004				
Δ% CO	0.47(0.35–0.60)	<0.001	0.28(0.03–0.52)	0.028		
Δ% SAP/ESV					−0.10(−0.20 to −0.01)	0.035
Δ% RVEDV	0.73(0.43–1.03)	<0.001				
Δ% RVSV	0.27(0.13–0.41)	<0.001	0.24(0.10–0.37)	0.002		
Δ% Ea	−0.73(−0.88 to −0.59)	<0.001	−0.88(−1.26 to −0.50)	<0.001	−0.37(−0.51 to −0.22)	<0.001
(Constant)	7.59(4.08–11.10)	<0.001	27.56(19.92–35.20)	<0.001	1.57(−4.39–7.53)	0.588
Δ% EF	0.64(0.53–0.75)	<0.001				
Δ% EDV	0.99(0.85–1.13)	<0.001	0.59(0.21–0.97)	0.004	0.37(0.19–0.54)	<0.001
Δ% Ea	−0.23(−0.32 to −0.13)	<0.001	−0.69(−1.0 to −0.35)	<0.001	−0.31(−0.42 to −0.20)	<0.001

Abbreviations: see Table 1.
* Only significant coefficients are reported.

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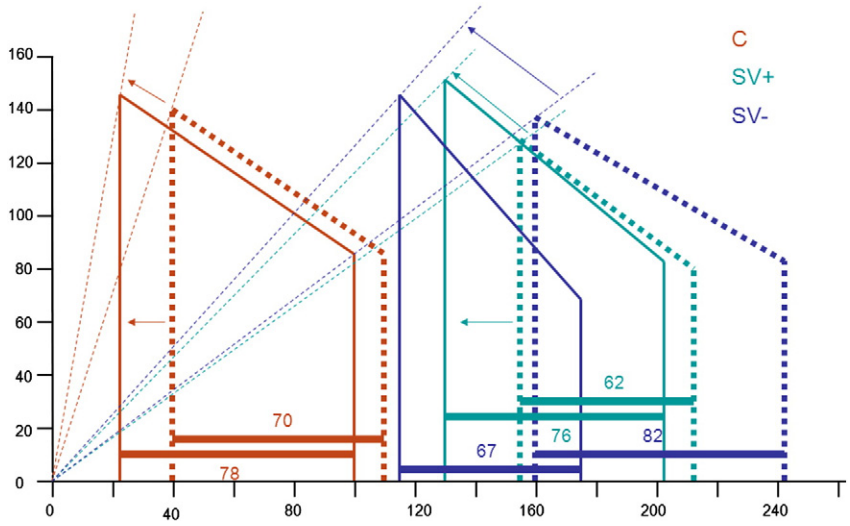

Fig. 3. Schematic representation of the results in the framework of the simplified pressure/volume model for non-invasive parameters. Average values of left ventricular end-diastolic and end-systolic volumes as well as of systolic and diastolic arterial pressures in the three groups studied, controls (C), DCM patients who increase stroke volume (SV+) and DCM patients who reduced stroke volume (SV−) during low dose dobutamine testing, are presented. Dotted thick line: resting; closed line: LDD.

contractility but rather of preload and afterload changes induced by the drug.

These results highlight that, in addition to direct cardiac effects mediated by its dominant beta agonist activity, dobutamine has vascular actions on both arterial and venous vessels, potentially affecting cardiac load, and thus cardiac performance. The direct action of dobutamine on the systemic venous system might play a critical role in modulating the ventricular preload overall, via stimulation of both alpha- and beta-adrenoreceptors [32,33].

Preload recruitment is the adaptive response to decreased myocardial contractility, in accordance with the Frank–Starling mechanism [17,34], and thus the lack of it might explain the absence of enhanced contractility during LDD infusion in SV− group. This assumes clinical relevance since LV-EF changes during LDD are recognized as an independent prognostic marker in patients with non-ischemic DC [14,15]. Moreover, the reduction in early ventricular filling can be mainly ascribed to preload changes rather than to impairment of left ventricle relaxation during acute increase in workload, as previously observed in hypertensive patients with LV diastolic dysfunction [35]. Previous studies showed that beta-adrenergic receptors might mediate venodilation in humans instead of venoconstriction. In our study we can assume that SV− patients might have an impaired venoconstrictive response in accord to previous report [36,37].

Moreover dobutamine also affects the afterloading characteristics of the systemic artery independent from the direct myocardial action [38]. The typical response to dobutamine is the reduction in afterload through the direct effect on the resistive arteriolar [38]. However, HF is characterized by several abnormalities of vascular function, including vasoconstriction, impaired exercise-induced vasodilation, and impaired endothelium-dependent vasodilation [39] that appear related in part to increased oxidative stress and reduced bioavailability of nitric oxide [40].

In particular the low availability of nitric oxide, that is the way through dobutamine produces vasodilation [41], may be one reason of the abnormal arteriolar vasoconstrictive response to dobutamine causing increased afterload, and thus impairment of stroke volume.

Thus taking at whole these results, we hypothesize that a vasoactive response to dobutamine, consisting of reduction in afterload (dilation of resistive artery) and increase in venous return mediated by a reduction in venous capacitance (constriction of capacitive vein) is elicited in control and SV+ patients. This vasoactive response provides the increase in cardiac performance in SV+ patients even in the presence of blunted contractile response. Conversely, this LDD-induced vasoactive reserve is blunted in SV− patients in whom the combination of reduced preload and increased afterload, and in the presence of blunted contractile response, impairs cardiac performance. Moreover it is also conceivable that SV− patients exposed to LDD, first exhaust the preload reserve since the EDV at baseline is higher than other groups. Consequently the higher LV-EF, and LV-SV, and the lower Ea and SVR in SV− as compared to SV+ are linked to expense of the preload reserve already at rest more than to a less impaired contractile reserve.

4.1. Limitations of the study

The small number of patients is the major limitation of the study. However, cardiac function and morphology were assessed by MRI that, allows accurate assessment of cardiac volumes and function with high reproducibility, enabling smaller sample size to reach statistical significance due to the high quality of imaging and the 3-D approach [9]. Another limitation of the study is the absence of invasive measurements of hemodynamic parameters not performed for ethical reasons, given the absence of clinical indication. In particular the invasive assessment of pressure/volume loop enables more comprehensive analysis of the interaction and relative contribution of the afterload and preload properties on changes in SV and EF.

4.2. Conclusions

In conclusion, we provided novel evidence that in a significant proportion of clinically stable patients with non-ischemic HF the response of LV-SV to LDD is not only dependent on the presence of contractile reserve, but can be also related to limited preload reserve, as well as to increased afterload.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [42].

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