ORIGINAL ARTICLE

Diastolic stress echocardiography and biomarkers in patients with preserved left ventricular ejection fraction and heart failure symptoms

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ABSTRACT

Background: Diastolic dysfunction (DD) is a diagnostic challenge in clinical practice.

Aim: Our study aimed to evaluate the value of diastolic stress echocardiography (DSE) and heart failure (HF) biomarkers in patients with preserved left ventricular ejection fraction (LVEF) and HF symptoms.

Methods: All the consecutive patients with HF symptoms, preserved LVEF, and suspected DD were examined on transthoracic echocardiography (TTE) and DSE using the protocol according to the American Society of Echocardiography recommendations. Moreover, blood samples were taken 30 minutes before and after DSE for the following lab markers: N-terminal pro-B type natriuretic peptide (NT-proBNP), mid regional pro-atrial natriuretic peptide (MR-proANP), and serum soluble ST2 receptor (ST2).

Results: The study group included 80 patients (mean [standard deviation, SD] age, 69 (8.1) years; 25% males) with dyspnea (New York Heart Association classification IIa — 53; IIb — 17; III — 10) and risk factors: hypertension (96%), diabetes (41%), obesity (56%), and known coronary artery disease (10%). The rest transthoracic echocardiography (TTE) showed preserved systolic function (mean [SD], LVEF 61.1 [10.5]%) and normal or indeterminate diastolic function. DSE revealed a positive result for diastolic dysfunction in 17 patients (21%). The receiver operating characteristic (ROC) analysis showed that age (the area under the curve [AUC], 0.725; P <0.01), left atrial volume indexed for body surface area [LAVI] rest (AUC, 0.722; P <0.01), E/e' rest (AUC, 0.790; P <0.01), and baseline NT-proBNP (AUC, 0.713; P <0.01) predicted positive DSE. Other parameters, including body mass index, baseline E/A, DT, or e' were not predictive of DSE results.

Conclusions: DSE revealed diastolic dysfunction in 21% of study patients and improved the diagnostic value of echocardiography. Rest NT-proBNP, but not MR-proANP and ST2, provided a diagnostic value for diastolic dysfunction.

Key words: diastolic stress test, stress echocardiography, NT-proBNP, MR-proANP, ST2

INTRODUCTION

Left ventricular (LV) diastolic function may be evaluated noninvasively using transthoracic echocardiography (TTE) [1]. The main symptoms suggesting diastolic dysfunction (DD) are dyspnea, exertional fatigue, or poor exercise tolerance. The key variables recommended for assessment of LV diastolic function include simple parameters of mitral inflow and annular velocities, peak velocity of tricuspid regurgitation jet, and the left atrial volume index (LAVI) [2]. However, rest TTE may provide borderline diastolic abnormalities or inconclusive data. The gold standard for the diagnosis of LV DD is invasive testing with direct left ventricular pressures and/or pulmonary capillary wedge pressure measurements [1, 3, 5]. Hence, this method is relatively rarely

WHAT'S NEW?

Diastolic dysfunction is a diagnostic challenge in clinical practice. Transthoracic echocardiography in rest may provide borderline diastolic abnormalities or inconclusive data. Therefore, the current European Society of Cardiology guidelines recommend diastolic stress echocardiography (DSE) in patients with heart failure symptoms and normal or indeterminate diastolic function. In our study, DSE revealed a diastolic dysfunction in every fifth patient with inconclusive rest echocardiography. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was the only lab marker that significantly increased early after the exercise. The utility of DSE was similar despite various clinical characteristics. Rest NT-proBNP, but not mid-regional pro-atrial natriuretic peptide (MR-proANP) and serum soluble ST2 receptor (ST2), was the only biomarker of heart failure predictive for exercise diastolic dysfunction with similar predictive value to age, rest left atrium volume index, and E/e' ratio.

used in clinical practice, especially with invasive measurements of the pressures during exercise stress. Therefore, the current European Society of Cardiology guidelines recommend diastolic stress echocardiography (DSE) in patients with heart failure (HF) symptoms and normal or indeterminate diastolic function [3]. A substantial number of patients with hypertension, diabetes, or LV hypertrophy, do not meet the criteria for DD on rest TTE [4].

The natriuretic peptides, including the N-terminal pro-B type natriuretic peptide (NT-proBNP) and mid regional pro-atrial natriuretic peptide (MR-proANP) are the most important lab markers of myocardial overload and strain. They are released to induce vasodilatation and diuresis [6].

Inflammation may be considered one of the mechanisms leading to LVDD [7]. ST2 is an inflammatory cytokine, which is involved in myocardial fibrosis, hypertrophy, and cardiac remodeling [8, 9]. All three cytokines are perceived as lab markers of left ventricular dysfunction and HF, which can improve the clinical diagnosis or prognosis [10].

NT-proBNP is a major natriuretic peptide used in clinical practice in contrast to the other two markers. Although the data on the pharmacotherapy of HF with preserved left ventricular ejection fraction (LVEF) are divergent and we look forward to further trial results, proper diagnosis will have an impact on the implementation of therapies that may improve exercise tolerance and quality of life [11].

Therefore, our study aimed to evaluate the clinical value of diastolic stress echocardiography (DSE) and blood markers of HF in patients with preserved LVEF and HF symptoms.

METHODS

Eighty consecutive patients with exertional dyspnea and suspected DD or borderline diastolic abnormalities on TTE were enrolled in the study.

The main exclusion criteria were as follows: HF with reduced ejection fraction (HfrEF; LVEF ≤45%), severe DD considered as a restrictive filling pattern on TTE at rest, significant valve disease (severe regurgitations, at least mild valve stenosis), atrial fibrillation, severe chronic kidney disease (glomerular filtration rate [GFR] <30 ml/min/1.73 m^2), acute cardiovascular diseases in prior 8 weeks (e.g. acute coronary syndrome, acute pulmonary embolism, stroke), significant chronic pulmonary diseases, acute infectious disease in prior 4 weeks.

For better characterization of functional capacity, we used a modified New York Heart Association [NYHA] classification with class II subgrouping in IIa class defined as dyspnea after running or climbing ≥2 flights of stairs, and IIb class as dyspnea after fast walking or climbing 2 flights of stairs [12].

A routine TTE screening was performed in all subjects at the enrollment, which followed the ASE guidelines [1, 13]. All the subjects were scheduled for exercise echocardiography limited by symptoms and fatigue, according to the ASE clinical recommendation, using a treadmill ergometer (Aspel, Cardiotest B612, Poland) [14]. TTE was performed at rest just before the exercise and at peak stress. The workload was escalated in a stepwise fashion adding 25W every 3 minutes according to the Bruce protocol [14]. DSE test was considered positive when the following conditions were met: average E/e' >14 and peak TR velocity >2.8 m/s [1].

A Philips HD15 ultrasound system (Bothel, WA, US) was used in all cases and anonymized echocardiographic data were stored digitally. All the SE tests were performed by one operator blinded to the lab tests results and analyzed offline.

Left ventricular diastolic dysfunction was assessed according to the ASE guidelines [1]. In brief, if more than 50% of the following parameters were abnormal (average E/e' >14, septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, TR velocity >2.8 m/s, and the LA volume index >34 ml/m^2), DD was confirmed. In other cases, diastolic function was indeterminate (50% of abnormal parameters) or normal (<50%).

The LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and LA — left atrial volume (LAV) parameters were assessed using a 2D Simpson's method. Transmitral inflow velocities and tissue Doppler parameters were obtained according to the guidelines [13].

The blood specimens were obtained 30 minutes before and 30 minutes after the SE in all the study patients. The following markers of HF were assessed: NT-proBNP, MR-proANP, and ST2 (BioVendro R&D, Cz).

The study was conducted at the Department of Cardiology at the Upper-Silesian Medical Center of the Medical University of Silesia in Katowice in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee (no. KNW/0022/KB1/76/17) and all subjects gave written informed consent before the study enrollment. This work was supported by a non-commercial research grant from the Medical University of Silesia (KNW-1-026-K/9/K).

Statistical analysis

Qualitative parameters are presented as numbers and percentages. Distributions of continuous variables were analyzed using the Kolmogorov-Smirnov test. All continuous variables normally distributed are presented as means and standard deviations (SD) and non-normally distributed as medians and interquartile ranges. Correlations between clinical, echocardiographic, and biochemical continuous parameters were tested using the Pearson coefficient correlation test. The Student's t-test, Mann-Whitney U test, χ^2 test, paired sample t-test, Wilcoxon signed-rank test, and McNemar's test were used where appropriate to test the differences among parameters and between groups. To determine the best cut-off of baseline parameters, the receiver operating characteristic (ROC) curves were used providing sensitivity, specificity, and optimal predictive values for diastolic dysfunction. A *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using MedCalc software (version 19.1).

RESULTS

The baseline characteristics of the study population are presented in Table 1. In brief, the study group included 80 patients (mean [SD] age, 69 (8) years; 25% males) with dyspnea (NYHA IIa — 53; IIb — 17; III — 10) and the following risk factors: hypertension (96%), obesity (56%), diabetes (41%), coronary artery disease (10%), and chronic kidney disease (26%). The rest TTE showed a preserved systolic function (mean [SD] LVEF, 61.1 [10.5]%) and normal or indeterminate diastolic function in all patients. Normal LV geometry was found in 19 (23%) patients and normal LV mass index in 48 subjects (60%). Most patients revealed either concentric remodeling (36%) or concentric hypertrophy (33%) of LV.

Table 1. Demographic and clinical characteristics of the study group

Age, years, mean (SD)	69 (8.1)
Male sex, n (%)	20 (25)
BMI, kg/m^2, mean (SD)	31.3 (4.9)
Obesity, n (%)	45 (56)
Hypertension, n (%)	77 (96)
Diabetes, n (%)	33 (41)
Dyslipidemia, n (%)	70 (87)
Nicotinism, n (%)	5 (6)
CAD, n (%)	8 (10)
Previous MI, n (%)	2 (2.5)
Previous PCI, n (%)	4 (5)
Previous CABG, n (%)	0
Cardiovascular pharmacotherapy	
β-blockers, n (%)	70 (87)
ACE-I, n (%)	54 (67)
ARB, n (%)	13 (16)
Aldosterone – antagonist, n (%)	5 (6)
Diuretics, n (%)	34 (42)
Calcium antagonist, n (%)	37 (46)
Nitrate, n (%)	1 (1.25)
Antidiabetic drugs, n (%)	17 (21.25)
Insulin, n (%)	8 (10)
Hypolipidemic drugs, n (%)	60 (75)

Abbreviations: ACE-I, angiotensin-converting inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 2 presents all the major echocardiographic parameters obtained at rest and peak stress during DSE. As expected, there were significant differences in most of the parameters, except for diastolic blood pressure, left ventricular end-diastolic volume, Tei index, and LAVI.

All the patients completed their DSE and positive results for diastolic dysfunction were found in 17 patients (21%).

Table 2. Echocardiography at rest and peak stress test

Variable	Rest	Stress	*P*-value
Heart rate, beats/min, mean (SD)	74.1 (10.4)	122.1 (17)	<0.001
SBP, mm Hg, mean (SD)	131.2 (16)	159.2 (21.1)	<0.01
DBP, mm Hg, mean (SD)	77.1 (8.5)	78.5 (7.1)	0.3
LV EDV, ml, mean (SD)	91.2 (29)	89.7 (29.3)	0.7
LVEF, %, mean (SD)	61.1 (10.5)	71.3 (9.2)	<0.0001
TDI Tei index, mean (SD)	0.37 (0.04)	0.38 (0.04)	0.7
E/A, mean (SD)	0.9 (0.47)	1.23 (0.47)	<0.0001
E/e', mean (SD)	11.5 (3.95)	13.9 (4.3)	0.001
TDI e', mean (SD)	6.1 (0.9)	8.1 (1.46)	<0.001
E/e'<7, n (%)	64 (80)	23 (28.7)	<0.0001
E/e'>14, n (%)	16 (20)	35 (43.8)	0.001
LAV index, mean (SD)	36.1 (9.2)	34.8 (9.5)	0.76
LAVI >34 ml/m^2, n (%)	40 (50)	41 (51)	0.9
TR Vmax >2.8 m/s , n (%)	11 (13.7)	27 (33.7)	0.01

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, end-diastolic volume; EF, ejection fraction; LAV, left atrial volume; LAVI, left atrial volume index; LV, left ventricle; SBP, systolic blood pressure; TDI, tissue Doppler imaging; TR, tricuspid regurgitation

Table 3. Laboratory markers of heart failure at rest and peak stress test

Variables	Rest	Stress	*P*-value
NT-proBNP, pg/ml, median (IQR)	273 (161–517)	317 (176–521)	<0.001
NT-proBNP >125 pg/ml, n (%)	64 (80)	67 (83)	0.6
MR-proANP, pmol/l, median (IQR)	16.8 (7.9–501.7)	15.3 (6.2–634.2)	0.5
MR-proANP >60 pmol/l, n (%)	24 (30)	25 (31)	0.9
MR-proANP >120 pmol/l, n (%)	24 (30)	25 (31)	0.9
ST2, ng/ml, median (IQR)	16.2 (12.1–21.5)	16.3 (12.6–21.1)	0.7
ST2 >35 ng/ml, n (%)	4 (5)	3 (3.7)	0.7

Abbreviations: MR-proANP, mid-regional pro atrial natriuretic peptide; NT-proBNP, n-terminal pro B-type natriuretic peptide

Table 4. Laboratory markers of heart failure — the comparison between the subgroup with (DD+) and without diastolic dysfunction (DD-) in stress echocardiography

Variable	Rest			Stress		
	DD (+) n = 17	DD (–) n = 63	*P*-value	DD (+) n = 17	DD (-) n = 63	*P*-value
NT-proBNP, pg/ml, median (IQR)	443.8 (316.2–781.2)	240.9 (142.1–438.7)	0.007	481.1 (343.3–824.8)	261.8 (158.2–492.3)	0.005
MR-proANP, pmol/l, median (IQR)	17.2 (8.4–598.2	14.9 (7.25–642.7)	0.4	17.1 (8.3–444.2)	14.7 (5.7–670.4)	0.53
ST2, ng/ml, median (IQR)	16.4 (12.2–18.7)	16.2 (12.1–23.6)	0.32	15.2 (12.6–19.9)	16.4 (12.5–22.4)	0.56

Abbreviations: DD, diastolic dysfunction; other — see Table 3

Table 5. The ROC analysis in the prediction of the diastolic dysfunction on stress echocardiography

Baseline parameters	AUC (95% CI)	*P*–value	Optimal value	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Patient's age, years	0.725 (0.613–0.819)	0.0004	>69	89	58	36	95
LAVI rest, ml/m^2	0.722 (0.610–0.816)	0.0016	>42	53	89	56	88
E/e' rest	0.791 (0.686–0.874)	0.001	>11	88	66	42	95
NT-proBNP rest, pg/ml	0.713 (0.601–0.809)	<0.01	>283.5	82	64	38	93

Abbreviations: see Tables 2 and 3

NT-pro BNP was the only lab marker of HF, which increased significantly after DSE (Table 3). The other markers (MR-proANP and ST2) revealed similar serum levels before and after DSE.

Afterward, patients were divided into two subgroups: with and without diastolic dysfunction (DD+ and DD-). Patients with DD revealed significantly higher NT-proBNP serum levels both before and after DSE (Table 4). However, MR pro ANP and ST2 serum levels were not different in both subgroups.

The study group was divided into subgroups based on age (<71 vs. ≥71 years), obesity, or diabetes. There were no differences between those subgroups in echocardiographic parameters of DSE obtained at rest or peak exercise (data not shown).

The NT-proBNP serum levels were significantly higher in the subgroup ≥71 years compared to subjects <71 years both at rest (median [interquartile range, IQR], 389 [228–589] pg/ml vs. 188.7 [83.1–388.5] pg/ml; *P* <0.001) and stress (median [IQR], 432.6 [262.4–600] pg/ml vs. 212.1 [97.3–392] pg/ml; *P* <0.001). Moreover, patients with normal LAVI showed significantly lower NT-pro BNP serum values compared to patients with enlarged LAVI: at rest (median [IQR], 238.7 (131–383.6) pg/ml vs. 398.1 (192–552.6) pg/ml; *P* = 0.01) and after stress (median [IQR], 260.2 [133.5–402] pg/ml vs. 442 [232.1–614.9] pg/ml; *P* = 0.01).

Moreover, NT-proBNP serum levels showed a significant association with LAVI at rest (r = 0.4; *P* = 0.001) and a trend towards association with patients' age (r = 0.2; *P* = 0.07). There was also a trend towards association between serum ST2 levels and the LV mass index (r = 0.2; *P* = 0.06). There was a positive correlation between stress NT-proBNP and stress LAVI (r = 0.3; *P* <0.05) and stress E/e' (r = 0.5; *P* <0.05).

Receiver Operating Characteristic analysis

The ROC analysis was performed to verify the predictive values of TTE parameters obtained at rest and lab markers for DD. It showed that age (AUC, 0.725; *P* <0.01), LAVI rest (AUC, 0.722; *P* <0.01), E/e' rest (AUC, 0.790; *P* <0.01), and baseline NT-proBNP (AUC, 0.713; *P* <0.01) predicted positive DSE (Table 5, Figure 1). The predictive values (AUC) of those baseline parameters were similar (*P* >0.05). Other parameters, including body mass index (BMI), baseline E/A, DT, or e' were not predictive for DSE results. Finally, if more than one of the baseline criteria were fulfilled, the sensitivity for DD was 100%.

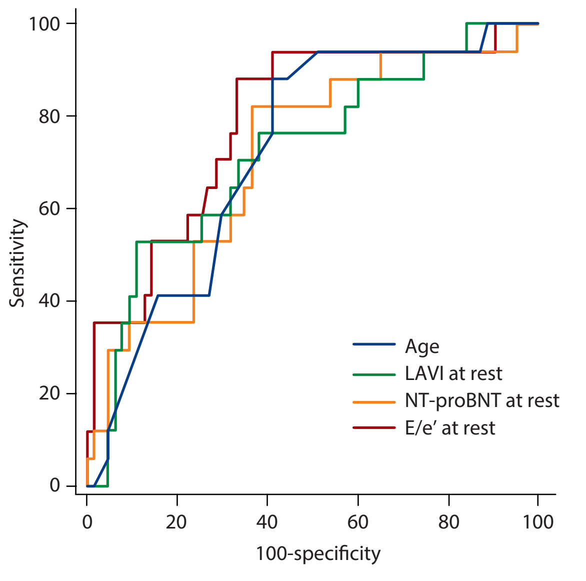

Figure 1. ROC analysis — diastolic stress echocardiography

Abbreviations: LAVI, left atrial volume indexed; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROC, receiver operating characteristic

DISCUSSION

Our study showed a few interesting findings important for clinical practice. First, DSE reveals a DD in every fifth patient with inconclusive rest TTE. Second, NT-pro BNP was the only lab marker, which significantly increased early after exercise echocardiography. Third, the utility of DSE was similar despite various clinical characteristics. Fourth, rest NT-proBNP was the only biomarker of HF predictive for exercise DD with a similar predictive value to age, rest LAVI, and E/e'.

In our study, DSE revealed DD in 21% of patients with HF symptoms and suspected DD or borderline diastolic abnormalities on rest TTE. There is considerable heterogeneity among other studies in the rates of abnormal LV diastolic function on exercise echocardiography related to study groups and various echocardiographic parameters used as markers of diastolic function [15, 16]. Therefore, the rates of positive diastolic stress tests varied from a few percent [17] to nearly half of the study group [18]. Nishi et al. [19] found that 16% of asymptomatic patients with DM and normal rest diastolic function showed a positive DSE. Gharacholou et al. [18] retrospectively analyzed a large group of 2835 patients, who had had exercise echocardiography. In the subgroup of patients with normal systolic function and no wall motion abnormalities, mild DD was noted in up to 40% of participants. Moreover, impaired exercise diastolic reserve was found to be more frequent in patients with DM [20]. DD is a key factor in the pathogenesis of HF. Frequently, symptoms of DD occur only during exercise, as LV filling pressure is normal at rest but increases with exercise [21]. Major risk factors for diastolic dysfunction include age, hypertension, diabetes mellitus, and LV hypertrophy [22]. Asymptomatic mild LV DD was found in 21%, and moderate or severe diastolic dysfunction is present in 7% of the population [23]. Diastolic filling can be compensated at the resting state, but the LV is unable to enhance diastolic filling and increase cardiac output without an abnormal elevation in left atrial pressure and pulmonary artery wedge pressure (PAWP) during exercise [24]. There are several patients in clinical practice with symptoms but with normal or indeterminate function in rest echocardiography. In these patients, it is important to evaluate filling pressure with exercise [25]. An important role of diastolic exercise echocardiography is to provide an accurate diagnosis of DD and HF [26]. The exercise echocardiography and the E/e' ratio were found to have a good correlation with LV filling pressures obtained simultaneously in cardiac catheterization [27]. Finally, DSE was found to predict clinical outcomes. The meta-analysis by Sud et al. found that exercise-induced DD was associated with a higher likelihood of cardiovascular mortality or hospitalization [15].

Our study showed that rest NT-proBNP predicted positive DSE, but stress NT-proBNP did not add a diagnostic value. Thus, rest levels of NT-proBNP helped to predict an exercise-induced DD. It could be used in addition to major echocardiographic indices of diastolic dysfunction (E/e', LAVI) in patients unable to perform an exercise protocol. In patients with normal left ventricular function at rest but elevated filling pressures at exercise, NT-proBNP levels were also found to be increased compared to controls with normal filling pressures at exercise [28, 29]. Similarly, there was an association of an elevated E/E'-ratio with increased BNP levels after exercise in patients with DD or suspected diastolic heart failure (DHF) [28, 30].

The other natriuretic peptide (MR-proANP) did not show any associations with DD and failed to predict exertional DD. Moreover, stress MR-proANP obtained early after the exercise load was also similar to its rest serum levels, which is in line with no significant changes in rest-stress LAVI. It also suggests that baseline MR-proANP does not have sensitivity to reflect DD in non-acute settings. Both natriuretic peptides are recommended to be used in clinical practice, especially in patients with acute dyspnea and suspicion of acute HF [3]. The increased NT-proBNP serum levels originate from the LV as a response to ventricular pressure and volume overload [31–33]. Atrial natriuretic peptide and the increased MR-proANP originate mainly from healthy and overloaded atria and also from the LV with systolic dysfunction [33]. Those differences in natriuretic peptides may explain our findings. Finally, the exact changes and dynamics of serum levels of natriuretic peptides in response to exercise load are unknown. So the optimum time to take blood after the exercise is also unknown and could affect our findings. Serum ST2 level is a novel marker of cardiac remodeling with suggested diagnostic (acute HF) and predictive (HF, death) values [10].

However, our study does not support the diagnostic value of ST2 in stable patients with exertional dyspnea and suspicion of DD. Serum levels of ST2 were not affected by exercise load, either. A clinical follow-up of the study patients will verify if baseline ST2 serum concentrations may provide any prognostic data.

CONCLUSIONS

DSE revealed DD in 21% of study patients and improved the diagnostic value of echocardiography. Rest NT-proBNP, but not MR-proANP and ST2, provided a diagnostic value towards DD. Our study may help to establish a strategy for the prediction and diagnosis of DD to explain patients' symptoms and HF with preserved ejection fraction. Further clinical follow-up should assess any predictive value of DSE and exertional lab markers of HF.

Article information

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