Myocardial strain may predict exercise tolerance in patients with reduced and mid-range ejection fraction

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Short Title: Strain analysis and exercise ability in heart failure

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ABSTRACT

Background: Conventional echocardiographic parameters, such as rest ejection fraction, perform poorly regarding the prediction of exercise tolerance in heart failure. The aim of the present study was to evaluate the contribution of hemodynamic instability in the observed lower functional capacity, investigating the role of left ventricular strain for the prediction of stress test duration in obese hypertensive patients with reduced ejection fraction.

Methods: Sixty-one patients with reduced ejection fraction underwent treadmill exercise echocardiography. Systolic and diastolic echocardiographic parameters were recorded. Moreover, the presence of hemodynamic instability was assessed through N-terminal pro B-type natriuretic peptide (NT-proBNP) measurements, at baseline and peak exercise.

Results: Rest and peak NT-pro BNP levels, and their difference, were significantly correlated with mean global strain at peak, which was the only parameter linked to changes in NT-proBNP levels. Rest and peak mean global strain were found to be predictive for the duration of treadmill stress test. In particular, mean global strain, but not left ventricular ejection fraction, was independently correlated with exercise ability.

Conclusions: Stress echocardiography may provide important information regarding the exercise tolerance in obese hypertensive patients with reduced ejection fraction, mainly through the evaluation of left ventricular strain. The obtained evidence may also have prognostic value, particularly in the early stages of the syndrome.

Keywords: *echocardiography; ejection fraction; exercise capacity; heart failure; NT-proBNP; strain analysis*.

1. INTRODUCTION

Heart failure (HF) is considered as a global pandemic affecting approximately 26 million patients worldwide [1]. It is associated with significant direct costs to healthcare systems, as well as indirect costs to society, mainly due to morbidity, premature mortality and lost productivity [2]. The annual HF-related hospitalizations exceed 1 million both in the United States and Europe [1]. Post-discharge mortality and re-admission rates continue to be high in hospitalized HF patients despite the advances in the management of the syndrome during the last decades. On the other hand, the prognosis of ambulatory HF patients with reduced left ventricular ejection fraction (LVEF) has been improved based on the discovery of various evidence-based drug and device therapies.

During peak exercise, sympathetic-mediated blood redistribution from non-exercising areas of the body to the working muscles, combined with metabolic-induced vasodilation, leads to higher blood flow at the sites of active muscles [3]. In HF patients, several mechanisms may contribute to the development of exercise intolerance. Although central parameters, such as LVEF, do affect exercise ability, peripheral factors seem to be mostly responsible for the reduction in exercise capacity [4]. There may be also some respiratory causes, such as structural pulmonary abnormalities (e.g. fibrosis) or poor inspiratory muscle performance. Notably, no single method can predict objectively the exercise tolerance in HF. Various compensatory mechanisms seem to preserve exercise ability despite the presence of LV dysfunction, and traditional predictors of LV function may be normal in a significant number of patients. In particular, LVEF has been found to predict poorly the exercise tolerance in HF [5-7]. Further, the relationship between exercise ability and LVEF may be influenced by various comorbidities, such as anaemia, hypertension or coronary artery disease (CAD). Consequently, resting echocardiography parameters are now considered as inaccurate predictors of exercise capacity in patients with HF.

Since its discovery more than 15 years ago, B-type natriuretic peptide (BNP) has emerged as an important biomarker in the diagnostic investigation and prognostication of HF patients; initial studies showed that BNP levels were highly related to impaired LV function [8-12]. BNP is mainly secreted in the heart ventricles due to ventricle volume expansion and/or pressure overload, in a pro form (pro-BNP). Once released from the heart, the N-terminal piece of the pro form (NT-proBNP) is rapidly cleaved by enzymes. In the present study, we investigated whether the lower functional capacity in HF patients with impaired LVEF is associated with the presence of hemodynamic instability, as assessed through NT-proBNP measurements. If so, the mean global strain at rest, indicating the global deformation of the myocardium, should have predictive value regarding the duration of the exercise test.

Therefore, the aim of the present study is to explore the relationship between exercise capacity and myocardial mechanics in order to investigate whether the exercise tolerance is more closely related to LV strain than to LVEF.

2. METHODS

This single-centre, cross-sectional study was conducted at the 2nd Department of Cardiology, Henry Dunant Hospital in Athens, Greece, over one year period (September 2015 – September 2016). We evaluated 82 consecutive HF patients referred to our department for clinical and echocardiographic assessment. Twenty one of the 82 patients were excluded from the study because they met at least one of the following exclusion criteria: acute coronary artery syndrome within the preceding 7 days, LV hypertrophy, moderate or severe valvular heart disease, atrial fibrillation, moderate or severe renal insufficiency (glomerular filtration rate, GFR <60mL/min), chronic obstructive pulmonary disease and anaemia.

The remaining 61 patients formed the study population Before testing, all subjects gave informed consent for their complete participation in the study, in compliance with the Hospital Ethics Committee guidelines. Moreover, a brief structured interview took place. Participants were clinically examined and assessed based on the New York Heart Association (NYHA) functional classification. Data regarding clinical features, previous cardiac events, CAD risk factors, and cardiac or non-cardiac comorbidities were recorded. Finally, blood samples were collected for NT-proBNP measurements at baseline and peak exercise.

2.1 Exercise Electrocardiography / Echocardiography

Treadmill exercise electrocardiography was performed according to standard techniques, as recommended by the American Heart Association (AHA) [13]. The Bruce protocol was applied using the Max 1 system (GE Marquette, Milwaukee, USA). Test results were evaluated according to the AHA guidelines criteria [13]. Functional capacity in METs was estimated using standard tables.

Echocardiographic evaluation was performed using Vivid 7 and Vivid E9 systems (GE Healthcare, Horten, Norway); data was analysed offline (EchoPAC®). All patients underwent transthoracic echocardiography at rest and within one minute after exercise. We calculated LV diameters by M-mode and LVEF according to the Simpson's biplane method. LV longitudinal strain was analysed by speckle tracking echocardiography, with frame rate ≥50s. From apical four-chamber, two-chamber, and long-axis view, peak longitudinal strains from each of the 16 LV segments, either negative or positive, were averaged to LV global longitudinal strain (mean global strain). Further, three diastolic function parameters were recorded; peak early diastolic filling (E) and late diastolic filling (A) velocities, and E/A ratio (Table 1).

2.2 Statistical Analysis

Quantitative variables are presented with mean and standard deviation (SD) and/or median (interquartile range=IQR). Qualitative variables are presented with absolute and relative frequencies. Pearson and Spearman correlations coefficients (r) were used to explore the n of two continuous variables. Correlation coefficient between 0.1 and 0.3 were considered low, between 0.31 and 0.5 moderate and those over 0.5 were considered high. Paired t-tests were used for the comparison of stress parameters among rest and peak exercise. Multiple linear regression analysis was used to explore the association of stress test duration and NT-proBNP with strain parameters and LVEF after adjusting for sex, age, smoking, body mass index (BMI) and hypertension. Adjusted regression coefficients (β) with standard errors (SE) were computed from the results of the linear regression analyses. Log transformations were made for NT-proBNP in regression analysis due to non-normal distribution. Global strain at rest, global strain at peak exercise, and their difference were examined separately in the linear regression models because of their high correlation. All reported p values are two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (version 19.0).

3. RESULTS

Study sample consisted of 61 patients (47 males, 14 females) with mean age 57.3 years (SD=11.1 years). Characteristics of the sample are presented in Table 1. Most of the patients were overweight (62.3%) or obese (21.3%). Family history was recorded in 78.7% of the participants and the presence of hypertension was demonstrated in about half of the study sample (49.2%). 37.7% of the patients were smokers. Moreover, cardiac resynchronization therapy (CRT) had been performed in 11.5% of the subjects. The majority of the participants suffered from dilated cardiomyopathy (85.2%), while 14.8% of the cases were of ischemic aetiology (14.8%).

Most patients were receiving recommended pharmacologic therapy for chronic heart failure 80% were receiving diuretics 88% were taking any dose of ACE inhibitors or ARBs, 82% were taking stable dose of a beta-blocker and 50% were taking MR antagonists.

The mean duration of the stress test was 6.3min (SD=2.2min) and the mean LVEF was 33.3% (SD=11.3%). Median NT-proBNP at rest was 146 (IQR: 98.0-225.0) and at peak exercise 224.0 (IQR: 148.0-337.2), indicating a median increase equal to 70 ($p<0.001$). Mean global strain was equal to -10.8 (SD=3.6) at rest and decreased to -13.9 (SD=5.6) at peak ($p<0.001$). The duration of stress test, NT-proBNP, LVEF and mean global strain at rest were similar between patients with dilated cardiomyopathy and those suffering from ischemic cardiomyopathy. Mean global strain at peak was significantly lower in those with ischemic cardiomyopathy ($p=0.039$).

Table 2 shows the correlation coefficients of the duration of stress test and NT-proBNP with strain parameters and LVEF. The duration of stress test was negatively correlated with mean global strain at rest, mean global strain at peak, as well as their difference (Fig. 1). Rest and peak NT-proBNP levels and NT-proBNP difference were significantly correlated with mean global strain at peak.

Adjusting the analysis for sex, age, hypertension, BMI and smoking via linear regression models (Table 3), mean global strain at rest, mean global strain at peak and their difference, but not LVEF, were found to be predictive for the duration of stress test. Moreover, mean global strain at peak was the only parameter associated with changes in NT-proBNP.

4. DISCUSSION

HF patients with reduced LVEF can show severe exertional symptoms and objective evidence of exercise intolerance [14]. Despite well-described abnormalities of central hemodynamic responses in HF, a poor correlation has been reported between parameters of resting ventricular function, and exercise tolerance [15]. In HF patients due to cardiomyopathy, Franciosa et al. showed that measures of resting LV performance were not linked to exercise capacity [16]. Also, Dubach et al. reported that high intensity exercise training did not affect rest LVEF in patients with reduced LV function [17]. Similarly, cardiopulmonary exercise testing was not found to be associated with LVEF [18]. Smart et al. noted that rest LVEF was poorly correlated to peak oxygen uptake (VO_2), which was more closely related to a composite model of filling pressure, systolic and diastolic function [19].

On the other hand, global longitudinal strain may perform better than LVEF in identifying patients with exercise intolerance. Strain echocardiography represents a valuable non-invasive imaging modality for the hemodynamic assessment of HF patients. Systolic function can be accurately quantified based on strain echocardiography, and Gjesdal et al. found that echocardiographic strain was superior to LVEF in the early detection of LV systolic function deterioration [20,21]. Further, a strong association between myocardial strain and exercise tolerance was demonstrated in HF patients with LVEF <40% [22]. However, Hasselberg et al. did not confirm such correlation between global longitudinal strain and exercise capacity in patients with reduced LVEF, a finding that may be associated with the heterogeneous underlying pathophysiologic mechanisms and co-morbidities in the advanced stages of systolic dysfunction [18].

Our results indicate that mean global strain is independently correlated to exercise capacity of obese hypertensive patients with reduced LVEF. In particular, mean global strain performed better than LVEF in identifying patients with impaired exercise tolerance. Therefore, strain analysis may be useful in discriminating patients with normal exercise capacity from those with moderate or severe exercise intolerance. Additionally, mean global strain at peak was the only parameter that was significantly correlated to changes in NT-proBNP. BNP is released by the ventricles under myocytic stretch and may indicate the presence of increased LV filling pressure, which is an important cause of exercise intolerance [23-25].

Moreover, echocardiographic strain has significant prognostic impact [26]. Haugaa et al. noticed that strain echocardiography may contribute to the risk stratification of patients suffering from dilated cardiomyopathy, while Stanton et al. reported that global longitudinal strain is better predictor of patient outcome in comparison to either LVEF or wall motion score index [27,28]. Interestingly, Hasselberg et al. showed that global longitudinal strain was the best parameter to identify patients with a peak VO_2 <20mL/kg/min [18].

Considering the strong relationship between exercise capacity and cardiac prognosis, our findings are in line with previous reports demonstrating the strong prognostic power of mean global strain [29,30]. Consequently, myocardial strain may have the potential to identify poor prognosis at early HF stages, in which the conventional echocardiographic parameters perform poorly. However, larger multi-centre studies are needed to confirm these encouraging findings regarding the role of strain analysis in the prediction of exercise tolerance and the prognostication of HF patients.

5. LIMITATIONS

Our study suffers from some limitations. The study sample is rather mixed; both overweight/obese and patients with normal weight (16.4%), and patients with reduced and mid-range ejection fraction were recruited. Moreover, the assessment of exercise tolerance was based on exercise duration. Other (more sophisticated) indexes of exercise capacity, such as the maximal oxygen consumption (VO_2max), % predicted heart rate, or the minute ventilation/carbon dioxide production (VE/VCO2) slope, were not used.

6. CONCLUSIONS

Despite well-described pathophysiological processes in HF with reduced LVEF, exercise tolerance of these patients cannot be accurately predicted based on a single method [31,32]. Among other factors, hemodynamic instability may contribute significantly to the observed exercise impairment. On the other hand, stress echocardiography can provide reliable data regarding several hemodynamic parameters. Using stress echocardiography techniques, we showed that mean global strain could predict exercise ability in obese hypertensive patients with reduced LVEF. Further, mean global strain measurements may contribute to the prognostication of HF patients, particularly at the early stages of the syndrome.

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Table 1: Study sample characteristics.

	N (%)		N (%)
Age, mean (SD)	57.3 (11.1)	Pacemaker	11 (18.0)
Gender		CRT	07 (11.5)
Males	47 (77.0)	LVIDd, mean (SD)	66.7 (8.9)
Females	14 (23.0)	LVIDs, mean (SD)	51.2 (7.5)
BMI, mean (SD)	27.9 (2.9)	EF, mean (SD)	33.3 (11.3)
BMI		Heart rate, mean (SD)	78.2 (12.0)
Normal	10 (16.4)	Duration of stress test	6.3 (2.2)
Overweight	38 (62.3)	WMA	
Obese	13 (21.3)	No	44 (72.1)
Family history		Yes	17 (27.9)
No	13 (21.3)	max SBP, mean (SD)	176.1 (21.8)
Yes	48 (78.7)	max DBP, mean (SD)	82.3 (7.4)
Smoking		E DOPPLER, mean (SD)	0.77 (0.23)
No	38 (62.3)	A DOPPLER, mean (SD)	0.7 (0.27)
Yes	23 (37.7)	E/A, mean (SD)	1.32 (0.8)
Hypertension		NT-proBNP at rest,	146.0
No	31 (50.8)	median (IQR)	(98.0-225.0)
Yes	30 (49.2)	NT-proBNP at peak,	224.0
Cardiomyopathy		median (IQR)	(148.0-337.2)
No	52 (85.2)	NT-proBNP difference	70.0
Yes	09 (14.8)	median (IQR)	(36.3-103.0)
Hypercholesterolemia		Mean global strain at rest,	-10.8 (3.6)
No	16 (26.2)	mean (SD)	
Yes	45 (73.8)	Mean global strain at peak,	-13.9 (5.6)
LDL, mean (SD)	127.7 (50.1)	mean (SD)	
HDL, mean (SD)	45.1 (21.2)	Global strain difference,	-3.03 (3.97)
Total cholesterol, mean (SD)	189.3 (49.5)	mean (SD)	

*BMI: body mass index; CRT: cardiac resynchronization therapy; DBP: diastolic blood pressure; EF: ejection fraction; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVIDd: left ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; NT-proBNP: N-terminal pro B-type natriuretic peptide; SBP: systolic blood pressure; WMA: wall motion abnormality

Table 2: Correlation coefficients of duration of stress test and NT-proBNP with global strain and ejection fraction.

		Stress test duration*	NT-proBNP at rest**	NT-proBNP at peak**	NT-proBNP difference**
Ejection fraction	r	-0.04	-0.10	-0.14	-0.11
	P	0.783	0.436	0.287	0.399
Mean global strain	r	-0.32	0.09	0.20	0.21
at rest	P	0.013	0.494	0.131	0.102
Mean global strain	r	-0.56	0.28	0.33	0.30
at peak	P	<0.001	0.031	0.010	0.019
Difference of global	r	-0.51	0.23	0.20	0.19
strain	P	<0.001	0.080	0.118	0.139

*Pearson's correlation coefficients, ** Spearmen's correlation coefficients

NT-proBNP: N-terminal pro B-type natriuretic peptide

Table 3: Multiple linear regression analysis results (dependent variables: duration of stress test and NT-proBNP changes).

		Stress test duration	NT-proBNP changes⁺
Ejection fraction	β (SE)*	0.001 (0.025)	0.001 (0.004)
	P	0.957	0.756
Mean global strain at rest	β (SE)*	-0.18 (0.07)	0.008 (0.013)
	P	0.019	0.549
Mean global strain at peak	β (SE)*	-0.23 (0.04)	-0.022 (0.011)
	P	<0.001	0.014
Difference of global strain	β (SE)*	-0.34 (0.06)	-0.021 (0.012)
	P	<0.001	0.083

*Regression coefficient (Standard Deviation), ⁺Analysis with log transformed values

NT-proBNP: N-terminal pro B-type natriuretic peptide

Figure 1

Scatter plot of difference of global strain from rest to peak exercise and duration of stress test.

Graphical abstract

Stress echocardiography may contribute to the prognostication of patients with heart failure. In obese hypertensive patients with reduced ejection fraction, the duration of stress test was negatively correlated with mean global strain at rest, mean global strain at peak, as well as their difference.