Usefulness of exercise tissue doppler echocardiography for prognostic stratification of congestive heart failure patients with left ventricular systolic dysfunction

Ondrej Ludka^a, Jan Trna^b, Lujza Galkova^a, Viktor Musil^a, Jindrich Spinar^a

Aim. Determination of the importance of exercise tissue Doppler echocardiography in prognostic stratification of congestive heart failure patients with systolic dysfunction.

Methods. 106 patients with congestive heart failure and LVEF $\leq 45\%$ on optimal pharmacotherapy were included in the study. Results of resting and post-exercise echocardiography, cardiopulmonary exercise test and serum BNP levels were available for all patients. Two patient groups were constituted, based on the prognostic classification. Group I contained 21 patients with poor prognosis (defined by predicted value of pVO₂ $< 76\%$ together with both VE/VCO₂ slope > 32.7 and BNP > 210 pg/mL) and group II with 85 patients who did not meet the criteria.

Results. The patient groups significantly differed in indexed volume of left atrium, mitral regurgitation severity, rest and post-exercise systolic velocity of mitral annulus and in rest and post-exercise E/Em. Multivariate analysis identified E/Em as the only independent predictor of prognosis. E/Em at rest (post-exercise) ≥ 16.6 (≥ 18.7) defined poor prognosis with sensitivity of 71% (86%) and specificity of 71% (71%).

Conclusion. Our study suggests usefulness of exercise tissue Doppler echocardiography for prognostic stratification of patients with congestive heart failure with possible superiority to resting parameters.

Key word: exercise echocardiography, heart failure, prognosis

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^aInternal Cardiology Department, University Hospital Brno and Faculty of Medicine, Masaryk University Brno, Czech Republic

^bInternal Gastroenterology Department, University Hospital Brno and Faculty of Medicine, Masaryk University Brno

Corresponding author: Ondrej Ludka, e-mail: oludka@fnbrno.cz

INTRODUCTION

Echocardiography represents an essential method in diagnostics, management and prognostic stratification of patients with chronic heart failure (CHF) (ref.¹). The interest in traditional heart function indicators such as left ventricular ejection fraction (LVEF), which has been shown to be of prognostic value in large cohorts of patients with CHF followed in extensive pharmacological studies^{2,3}, has shifted with technical progress and new echocardiographic methods to newer parameters assessing left ventricular diastolic function⁴, left ventricular filling pressure⁵, or systolic and diastolic right ventricular function⁶.

Recent attention has been brought to the evaluation of resting and postexercise heart function parameters in a more comprehensive way than simply the comparison of LVEF. Some studies indicate better potential of exercise echocardiographic parameters as for function capacity^{7,8}. Potential significance of exercise echocardiography likely results from the fact, that a significant portion of CHF patients are symptomatic mainly during exercise and function capacity is a standard examination algorithm in prognostic stratification when considering heart transplantation¹. Treatment management can be greatly influenced by knowledge about left ventricular exercise

reaction. The target of our work has been the evaluation of exercise tissue Doppler echocardiography in prognostic stratification of CHF patients and the measurement of its specificity and sensitivity compared to parameters obtained during only resting studies.

MATERIAL AND METHODS

We studied 106 heart failure patients with LVEF $\leq 45\%$ with dilatation cardiomyopathy or ischemic heart disease, who were recommended to pass the ergometry test for clinical indications by their heart failure specialist. The clinical research ethics committee approved this study, and all subjects signed informed consent.

Enrollment criteria included age over 18, history of heart failure ≥ 6 months, clinically stable condition ≥ 3 preceding months, acute coronary syndrome or elective myocardial revascularization ≥ 6 months, good echocardiographic examinability, ability to pass ergometry and optimal heart failure pharmacotherapy according to latest guidelines¹ providing there was no contraindication or intolerance, and the willingness of the patients to participate in this study.

Exclusion criteria have been defined as severe disorder of ventilation (corticoid therapy necessity or presence

of respiratory insufficiency at rest), ischemic response to exercise that passes the definition of a new kinetic disorder, valvular dysfunction of at least mild severity (in case of mitral regurgitation $ERO > 0.2 \text{ cm}^2$ regardless to etiology of the pathology), hypertrophic or restrictive cardiomyopathy, anemia (hemoglobin $< 120 \text{ g/L}$ for women, and $< 130 \text{ g/L}$ for men), assessed glomerular filtration $< 30 \text{ mL/min}$ (according to Cockcroft-Gault formula) and presence of pacemaker or implantable cardioverter-defibrillator.

Enrollment criteria have been met by 106 patients of average age of 64.1 ± 13.4 years, 20 (19%) were female.

Protocol consisted of clinical examination, blood sampling at standard conditions from the cubital vein for haemathologic and biochemic examination with determining the BNP level. Determination of the BNP level was carried out at the University hospital Brno central laboratory within 20 min of the blood sample collection. Diagnostic sets Axsym from Abbott were used for assessment. Afterwards, the patients underwent resting echocardiographic examination with bicycle spiroergometry. The exercise pulse Doppler and tissue Doppler echocardiography were recorded immediately after the exercise test.

Exercise spiroergometry test was carried out at Ergoline 900 ergometer using Jaeger Oxycon Delta, Erich Jaeger GmbH system for expired gases analysis. Its sensors were calibrated with a gas of known nitrogen, oxygen and carbon dioxide concentration before every test. The flow rate sensor was calibrated before every test, too. We used a ramp protocol with continuous increase of 10 W/min . Peak values were calculated as the average of a 30 s interval before the exercise end, and besides the absolute values (in mL/kg/min) we also calculated the percentage ratio adjusted to the subject's age and gender. Exercise test was drawn up as maximal, symptom limited. For calculation of parameter VE/VCO_2 slope we used 10 s averages of minute ventilation (VE) and rate of elimination of carbon dioxide (VCO_2) in the linear part of the VE (ax Y) VCO_2 (ax X) curve that were processed as two corresponding (time synchronized) columns in Microsoft Excel and using the "slope" function the calculation of parameter value (Fig. 1) was executed.

Basic echocardiographic measurements were carried out according to latest guidelines of American Society of Echocardiography⁸. LVEF was calculated according to biplanar disc method, left atrial volume according to biplanar method length-width in 4-chamber and 2-chamber apical projection. The values were indexed to the body surface.

Mitral regurgitation was calculated by PISA method⁹ (group 1 with no or trace regurgitation, group 2 with regurgitation orifice area $ROA < 0.1 \text{ cm}^2$ and group 3 with $ROA < 0.2 \text{ cm}^2$). Wave E of early mitral flow was measured at rest or after exercise by pulse Doppler using 5mm sampling volume positioned at the level of free mitral valve point edges in diastole. Myocardial speeds were set during rest and after exercise with tissue Doppler imaging (TDI) using 2 to 5 mm sampling volume positioned at the lateral and septal mitral annulus and lateral tricuspid annulus, Nyquist limit was set to $15\text{--}20 \text{ cm/s}$. Systolic wave (Sm

during rest and Sm' after exercise) and early diastolic mitral annulus wave (Em during rest and Em' after exercise) were calculated as the measurement average of septal and lateral mitral annulus regarding the present focal kinetic dysfunctions by great number of patients¹⁰⁻¹². Systolic tricuspid annulus wave (Stri) was measured only during rest. All the postexercise Doppler measurements were realized between the 2nd and 5th minute after the exercise test end¹²⁻¹⁴. after the end of the standard projection record for left ventricle kinetics assessment. We calculated the average of 3 measurements of patients with sinus rhythm and of 5 measurements of patients with atrial fibrillation.

Comparison of the groups in catheterial parameters was carried out with Fisher exact tests. Metric data was tested with Shapiro-Wilks normality tests. Parameters where the normal distribution was determined were processed with parametric Student t-tests. The majority of quantitative data wasn't characterized by normal distribution, comparing the groups in these parameters was carried out with nonparametric Mann-Whitney tests. Logistic regression in forward stepwise likelihood ratio organisation was used for multidimensional analysis to identify the independent predictors of poor prognosis. The independent variables, which demonstrated statistically significant difference in univariant testing between the compared groups, were characterised by the logistic regression. Colinearity between the independent predictors entering the multidimensional analysis was eliminated by VIF testing (variation inflation factors) with the critic value of 5. Reliability of the models was compared using Nagelkerke R^2 coefficient. Optimal cut-off value of the independent variable was searched using the ROC curves for prediction of prognostically poor result. All the tests were carried out on statistic significance level $P=0.05$. Statistically significant significance levels are highlighted in bold in the tables.

Group was divided into two parts (group I and II). Group I consisted of patients with prognostically poor finding defined as simultaneous presence of following values:

1. The actual oxygen consumption rate lower than the median (76 percent of the appropriate value)
2. VE/VCO_2 slope higher than median (32.7)
3. BNP higher than median (210 pg/mL)

The group consisted of patients with low oxygen consumption, high VE/VCO_2 slope and high BNP level. Group II comprised of all the other patients not meeting the criteria for the group I.

RESULTS

Table 1a,b summarizes demographic characteristics, comorbidities, treatment and function class NYHA patients in both groups.

Table 2 depicts exercise parameters and renal functions in both groups.

Echocardiographic parameters in both groups during

Table 1a,b. Demographic characteristics, comorbidities, treatment and function class NYHA in both groups.**Table 1a**

Parameter	Group I(N = 21)		Group II (N = 85)		<i>P</i>
	Median (Interval)	Mean $\pm$ SD	Median (Interval)	Mean $\pm$ SD	
Age (year)	70.0 (45-83)	67.4 $\pm$ 10.3	65.0 (32-85)	63.2 $\pm$ 13.9	0.291 ^b
BMI (kg/m ²)	27.1 (19.1-34.3)	27.1 $\pm$ 4.0	27.8 (18.3-41.8)	28.2 $\pm$ 4.8	0.536 ^b

^b Mann-Whitney test**Table 1b**

Parameter	Category	Group I (N=21) No. (%)	Group II (N=85) No. (%)	<i>P</i>
Sex	Men	16 (76.2)	70 (82.3)	0.539 ^a
	Women	5 (23.8)	15 (17.7)	
Etiology of CHF	DCMP	6 (28.6)	44 (51.8)	0.086 ^a
	CAD	15 (71.4)	41 (48.2)	
Diabetes mellitus	Yes	9 (42.9)	26 (30.6)	0.308 ^a
	No	12 (47.1)	59 (69.4)	
Hypertension	Yes	16 (76.2)	48 (56.5)	0.135 ^a
	No	5 (23.8)	37 (43.5)	
Atrial fibrillation	Yes	6 (28.6)	12 (14.1)	0.190 ^a
	No	15 (71.4)	73 (85.9)	
Furosemide	Yes	20 (95.2)	76 (89.4)	0.683 ^a
	No	1 (4.8)	9 (10.6)	
Spironolactone	Yes	14 (66.7)	54 (63.5)	1.0 ^a
	No	7 (33.3)	31 (36.5)	
ARB/ACEI	Yes	20 (95.2)	84 (98.8)	0.358 ^a
	No	1 (4.8)	1 (1.2)	
Betablocker	Yes	20 (95.2)	84 (98.8)	0.358 ^a
	No	1 (4.8)	1 (1.2)	
Statin	Yes	19 (90.5)	51 (60.0)	0.009 ^a
	No	2 (9.5)	34 (40.0)	
NYHA	1	7 (33.3)	22 (25.9)	0.038 ^a
	2	9 (42.9)	57 (67.1)	
	3	5 (23.8)	6 (7.0)	

^a Fisher exact test

NYHA 1 (NYHA <II) NYHA 2 (NYHA II and II-III) NYHA 3 (NYHA III and III-IV)

Table 2. Exercise parameters and renal functions in both groups.

Parameter	Group I(N = 21)		Group II (N = 85)		<i>P</i>
	Median (Interval)	Mean $\pm$ SD	Median (Interval)	Mean $\pm$ SD	
pVO ₂ [mL/kg/min]	11.4 (7.3-19.1)	12.5 $\pm$ 3.1	19.2 (9.4-39.9)	19.6 $\pm$ 5.7	<0.0001^b
Work tolerance [W/kg]	1.00 (0.60-1.60)	0.99 $\pm$ 0.28	1.26 (0.4-2.04)	1.54 $\pm$ 0.21	0.005^b
RER	0.98 (0.81-1.40)	1.02 $\pm$ 0.14	1.01 (0.80-1.38)	1.01 $\pm$ 0.13	0.978 ^b
GFR [mL/min]	60 (30-105)	58 $\pm$ 19	77 (30-156)	77 $\pm$ 30	0.005^b

^b Mann-Whitney test**Table 3.** Echocardiographic parameters in both groups during rest (without index) and after exercise (with index ').

Parameter	Group I(N = 21)		Group II (N = 85)		<i>P</i>
	No.	(%)	No.	(%)	
MR 1/2/3	9/9/3	42.9/42.9/14.2	67/13/5	78.8/15.3/5.9	0.004^a
	Median (Interval)	Mean $\pm$ SD	Median (Interval)	Mean $\pm$ SD	<i>P</i>
EDVi [mL/m ²]	105.0 (53.3-173.6)	106.6 $\pm$ 34.2	93.5 (55.6-195.5)	103.2 $\pm$ 32.1	0.649 ^b
ESVi [mL/m ²]	74.1 (32.1-133.1)	76.1 $\pm$ 30.8	61.6 (31.6-153.5)	69.3 $\pm$ 27.6	0.381 ^b
EF [%]	29.1 (16.7-44.1)	30.6 $\pm$ 8.8	34.8 (14.7-44.9)	34.2 $\pm$ 6.8	0.09 ^c
LAvoli [mL/m ²]	54.6 (28.1-81.9)	55.9 $\pm$ 13.8	41.6 (16.9-106.1)	45.4 $\pm$ 17.2	0.002^b
Sm [cm/s]	4.1 (2.5-9.4)	4.46 $\pm$ 1.61	5.80 (3.0-10.00)	5.96 $\pm$ 1.37	0.00004^c
S tri [cm/s]	9.2 (5.2-14.4)	9.78 $\pm$ 2.55	10.2 (5.4-18.0)	10.94 $\pm$ 2.54	0.065 ^b
E/Em	22.9 (9.7-40.7)	23.8 $\pm$ 9.6	12.9 (5.4-49.3)	14.3 $\pm$ 6.7	0.00003^b
Sm' [cm/s]	5.0 (3.1-11.4)	5.5 $\pm$ 2.2	7.8 (3.9-14.4)	7.6 $\pm$ 1.9	0.00002^b
E'/E'm	26.5 (10.3-44.4)	27.4 $\pm$ 9.3	15.6 (6.0-44.4)	16.7 $\pm$ 7.0	0.000002 ^b

^a Fisher exact test, ^b Mann-Whitney test, ^c Student t-test**Table 4.** Prediction of prognostically poor state with resting TDI parameters.

Model	Parameter	Odds ratio	95% CI		<i>P</i>	R ²
			Lower limit	Upper limit		
TDI at rest	E/Em rises by 5 unit	1.961	1.397	2.755	<0.001	0.275 ^a

^a Nagelkerke R²**Table 5.** Prediction of prognostically poor state using after exercise TDI parameters.

Model	Parameter	Odds ratio	95% CI		<i>P</i>	R ²
			Lower limit	Upper limit		
TDI after exercise	E'/Em' Rises by 5 unit	2.085	1.485	2.929	<0.001	0.330 ^a

^a Nagelkerke R²

Table 6. Optimal cut-off values for investigated predictors.

Model	Parameter	AUC	95% AUC		<i>P</i>	cut-off	sensitivity	specificity	Nagelkerke R^2
			Lower limit	Upper limit					
TDI at rest	E/Em	0.797	0.692	0.901	<0.001	≥ 16.6	71%	71%	0.275
TDI after exercise	E'/Em'	0.837	0.742	0.933	<0.001	≥ 18.7	86%	71%	0.330

Fig. 1. Relation between sensitivity and specificity for investigated predictors.

rest (without index) and after exercise (with index ') is summarized in Table 3.

Using multivariate analysis we created model A consisting of Doppler variants during rest and model B with Doppler variants after exercise.

Multivariate analysis was entered by those independent echocardiographic variables which differed significantly between both groups in univariate analysis. Moreover, the models were entered by glomerular filtration (GFR).

Model A: prediction of prognostically poor state with resting TDI parameters.

The analysis consisted of the following parameters: MR, GFR, LAVoli, Sm, E/Em. The dependent variable was the presence in group I – i.e. the presence of prognostically poor state.

Model chose one variable, that has the biggest influ-

ence on the dependent variable – E/Em. Interpretation of estimated model coefficients:

If the value of E/Em rises by 5, the odds of prognostically poor state rise 1.961 times (Table 4).

Model B: prediction of prognostically poor state using after exercise TDI parameters.

The analysis consisted of the following parameters: MR, GFR, LAVoli, Sm', E'/Em'. The dependent variable was the presence in the group I – i.e. the presence of prognostically poor state.

Model chose one variable with the biggest influence on the dependent variable – E'/Em'.

Interpretation of estimated model coefficients:

If the value of E'/Em' rises by 5, the odds of prognostically poor state rise 2.085 times (Table 5).

Using the ROC curve (Fig. 1) showing the relation between sensitivity and specificity for all the possible values of numeric parameter we defined the optimal cut-off values for investigated predictors (Table 6).

DISCUSSION

Combination of low functional capacity, ventilation exercise inefficiency and high levels of BNP helps in identification of patients with poor prognosis (group I) by taking more pathophysiologic mechanism into account which participate as pathogenic factors in CHF patients. A cross-sectional study of this type doesn't work with data like mortality planned study, however with regard to the size of our group and some distortions and inaccuracies connected to backward identification of death causes¹⁵ we preferred the above mentioned methodics of data processing.

Average value of pVO₂ in prognostically poor group of patients (group I) was $0.56 \pm 0.14\%$ (which corresponded to 12.5 ± 3.1 mL/kg/min). The majority of patients belonged to the gray zone regarding the usage of peak oxygen consumption in prognostic stratification of patients with CHF (ref.^{16,17}). From this perspective the simultaneous usage of pVO₂ and VE/VCO₂ slope by classification of patients from both groups according to assumed prognosis seems to be of great benefit¹⁸.

Every patient in group I had the VE/VCO₂ slope higher than 32.7. Considering the fact, that 95% of patients used a betablocator, we can summarise, that this parameter-wise the cut off value used corresponding to the median was of clinical relevance, too^{19,22}.

There is no generally accepted level of BNP by stable heart failure patients with optimal medical therapy which would clearly present a dividing line for prognosis setting. Criterium of BNP being higher than median, which was 210 pg/mL, corresponds relatively well with the values characterising poor prognosis in relatively comparable data files^{23,24}. These data confirm the significance of present BNP and pVO₂ use in prognostic stratification²⁴. Undeniable influence on the BNP is to be accounted to a high prevalence of renal insufficiency in our group²⁵ where 38% of patients had GFR < 60 mL/min. However, it does not diminish the information value of the high level of BNP as a predictor of unfavourable prognosis, as the renal insufficiency itself worsens the prognosis of these patients²⁶.

For identification of patients with poor prognosis (group I) we can state, that the cut-off values used in all the parameters correspond to earlier verified prognostic boundary values. It should enable selection of prognostic poor patients with acceptable sensitivity, on the other hand using of three objective parameters together contributes to the presumption of a good selection specificity. Similar to other authors we observed a difference between the patients of the two groups characterized by the tissue Doppler parameters of left ventricle longitudinal function during rest and after exercise, by the

ratio E/Em, indexed left ventricle volume and the level of mitral regurgitation^{5,11,27-29}. In both of our models the only independent echocardiographic predictor of a poor prognosis, similarly to other published data^{5,11}, was the parameter E/Em (during rest or after exercise). Adding other parameters into both models did not improve their discriminative ability any further. It is probably caused by the fact, that these parameters either reflect the same left ventricular diastolic dysfunction or the left ventricular filling pressure³⁰ respectively, or they influence each other to a certain extent^{31,32}. As shown by the ROC analysis, the difference in the prognostic accuracy between resting and post-exercise cutoff E/Em ratios is expressed mainly in the area of middle values. Within the range of 12-17 of resting E/Em ratio all the cut-off values demonstrate lower accuracy in the prognostic stratification of our group of patients in comparison with cut-off post-exercise E'/Em' values within the range of 15-21. We consider this as a clinically important finding, because the previously published works defined the optimal resting E/Em poor prognosis prediction cut-off in the range of 12-16^{5,11,33}. We reached a practically same conclusion for the value of 16.6.

The only so far published work comparing the resting and exercise E/Em ratio in the prediction of function capacity of patients with heart failure concludes, that the E/Em ratio at the peak of the exercise higher than 18.2 predicted a peak oxygen consumption lower than 14 mL/kg/min with sensitivity of 85.2% and specificity of 95.6% (ref.³⁴). These authors enrolled only patients with ischemic heart failure etiology and with sinus rhythm. Remarkably, in our work the post-exercise E/Em value of ≥ 18.7 was the optimal cut-off for prediction of not only of low function capacity, but also more complex combined poor prognosis indicator.

LIMITATION

Patients with mitral regurgitation with calculated ERO > 0.2 cm² were excluded because of the possibility of distortion of E/Em and left ventricular filling pressure relationship¹². Thus the conclusions of our work should not be applied for patients with serious ischemic or secondary mitral regurgitation.

The right ventricular function (assessed using the maximal systolic tricuspidal annulus movement speed) was not included in multidimensional analysis because patients in both groups showed borderline nonsignificant difference in this parameter. In both groups it was lower than 10.8 cm/s. These values were related with poor prognosis previously by Meluzin et al.³⁵

We investigated rather heterogeneous group of patients of wide age range, suffering from either ischemic or nonischemic etiology of heart failure, high prevalence of renal insufficiency and partially with atrial fibrillation. These facts could influence the sensitivity and specificity of tested parameters. On the other side our results reflects more closely the daily practise.

CONCLUSIONS

In our work we confirmed the significance of the E/Em parameter in prognostic stratification of patients with heart failure and its superiority over traditional echocardiographic parameters. Further, our results indicate a better potential of post-exercise measurement of this parameter in prognostic stratification of patients with heart failure with depressed left ventricular systolic function.

ABBREVIATIONS

BNP, B-type of natriuretic peptide; CAD, Coronary artery disease; CHF, Chronic heart failure; DCMP, Dilatative cardiomyopathy; E, Peak velocity of early diastolic filling of mitral inflow at rest; E', Peak velocity of early diastolic filling of mitral inflow after exercise; EDVi, End-diastolic left ventricular volume indexed to body surface; Em, Average of peak early diastolic velocity of the septal and lateral mitral annulus at rest; Em', Average of peak early diastolic velocity of the septal and lateral mitral annulus after exercise; ERO, Effective mitral regurgitant orifice area; ESVi, End-systolic left ventricular volume indexed to body surface; GFR, Glomerular filtration according to Cocroft-Gault formula; LAVoli, Left atrial volume indexed to body surface; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; pVO₂, Peak oxygen consumption; RER, Respiratory exchange ratio; Sm, Average of systolic velocity of the septal and lateral mitral annulus at rest; Sm', Average of systolic velocity of the septal and lateral mitral annulus after exercise; Stri, Systolic velocity of tricuspid annulus; TDI, Tissue Doppler imaging; VCO₂, Rate of elimination of Carbon Dioxide; VE, Minute ventilation; VO₂, Oxygen uptake.

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