Original article

Restrictive filling pattern predicts pulmonary hypertension and is associated with increased BNP levels and impaired exercise capacity in patients with heart failure

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Abstract

Background: Left ventricular (LV) diastolic dysfunction is a common finding in patients with systolic heart failure (HF). Severe diastolic dysfunction, which is defined as LV restrictive filling pattern (RFP), is associated with more severe HF, increased sympathetic activity and reduced exercise capacity. It has also been shown to be a predictor of lower survival rate in patients with HF.

Aim: To evaluate associations between LV diastolic RFP and BNP levels, systolic pulmonary pressure and exercise capacity in patients with clinically stable HF.

Methods: In 56 patients with HF and low LVEF a standard echocardiographic study and cardiopulmonary exercise test were performed. Levels of BNP using RIA method were also measured.

Results: Restrictive filling pattern (E/A >2 or 1< E/A <2 and DTE ≤130 ms) was diagnosed in 26 patients. The RFP group showed increased levels of BNP (90.6±66 vs. 50.4±61 pg/ml; p=0.003), significantly reduced peak VO_2 (15.4±4.1 vs. 17.8±4.9 ml/kg/min; p=0.046), increased VE/VCO_2 slope (36.3±5.9 vs. 31.9±6.3; p=0.01), and elevated PASP (pulmonary artery systolic pressure measured by echo-Doppler) (49.3±13.8 vs. 37.2±12.6 mmHg; p=0.02). Prevalence of pulmonary hypertension was significantly higher in the RFP group. A significant correlation between DTE and peak VO_2 (r=0.28; p=0.02) and inverse correlations between DTE and BNP levels (r=–048; p=0.003), VE/VCO_2 slope (r=–0.35; p=0.02) and PASP (r=–0.39; p=0.03) were found. In logistic regression analysis only RFP was independently associated with pulmonary hypertension.

Conclusions: The restrictive filling pattern is an independent predictor of pulmonary hypertension and is associated with increased BNP levels and worse result of cardiopulmonary exercise test.

Key words: heart failure, diastolic dysfunction, BNP, pulmonary hypertension, cardiopulmonary exercise test

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Left ventricular (LV) diastolic dysfunction is a common finding in patients with systolic heart failure (HF). Severe diastolic dysfunction, which is defined as LV restrictive filling pattern (RFP), is associated with more severe HF, increased sympathetic activity [1] and reduced exercise capacity [2, 3]. It has also been shown to be a predictor of lower survival rate in patients with HF [2, 4].

Heart failure is also characterised by elevated natriuretic peptides levels [5]. Plasma BNP levels provide prognostic information in patients with HF [6]. Recently, their association with diastolic dysfunction has been discussed [7].

Pulmonary hypertension (PHT) is a frequent finding in patients with systolic HF and is an important predictive marker of adverse outcome [8]. Left ventricular diastolic dysfunction has been suggested to be an important determinant of PHT in patients with HF [9, 10].

The aim of this study was to evaluate in clinically stable patients with systolic LV dysfunction whether the presence of diastolic RFP modifies BNP levels and

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influences systolic pulmonary pressure as well as exercise capacity.

Methods

Patients

The study group consisted of 56 patients with chronic HF referred to our department for diagnostic evaluation. The patients were in sinus rhythm with LV ejection fraction (LVEF) <45% (mean age 51.4±9.9 years, LVEF – 26.1±7% and NYHA functional class – 2.5±0.8). Ischaemic cardiomyopathy was diagnosed in 29 (52%) patients (history of myocardial infarction and/or >50% stenosis of at least 1 major epicardial branch at angiography) and dilated non-ischaemic cardiomyopathy in 27 patients. At the time of examination patients were in stable clinical condition for at least 2 weeks. Patients with chronic or acute inflammatory disease, severe pulmonary disease, severe renal insufficiency, atrial fibrillation or paced rhythm were excluded. All patients were maintained on their current HF therapy with stable doses for at least two weeks before the study. Fifty-two (93%) patients received angiotensin-converting enzyme inhibitors, 46 (82%) furosemide, 36 (49%) spironolactone, 28 (50%) digoxin, 41 (73%) beta-blockers, 33 (59%) aspirin, and 25 (45%) statins.

The study protocol was approved by the local Ethics Committee of the University of Medical Sciences and informed consent was obtained from each patient.

Echocardiography

All patients underwent 2D and Doppler echocardiography with a Hewlett-Packard Sonos 5500 device and 2.5 MHz transducer. Left ventricular ejection fraction was calculated from a 4-chamber view with modified Simpson's algorithm. Doppler recordings from the mitral inflow were obtained from the apical 4-chamber view to assess LV filling pattern. We evaluated peak early (E wave) and late (A wave) transmitral velocities, E/A ratio, and deceleration time of E wave (DTE). Left ventricular RFP was defined as E/A ratio ≥2 or between 1 and 2 with DTE ≤130 ms. Pulmonary artery systolic pressure (PASP) was estimated by continuous wave Doppler as the peak systolic pressure gradient across the tricuspid valve (in patients with detectible tricuspid insufficiency) plus right atrial pressure (estimated as 10 mmHg). Pulmonary hypertension (PHT) was defined as PASP ≥35 mmHg.

Exercise capacity

All patients underwent maximal cardiopulmonary exercise treadmill test according to the modified Bruce protocol. The peak oxygen consumption (peak VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured by breath-by-breath technique, using Sensor Medics, model Vmax29. The system was calibrated with a standard gas mixture of known concentration before each test. A standard 12-lead ECG was continuously recorded. All tests were terminated because of fatigue and/or dyspnoea. No test was terminated because of angina or arrhythmia. Peak VO_2 was determined as an average value during the last 20 s of exercise. The VE/VCO_2 slope was analysed as an index of excessive exercise ventilation.

BNP assessment

Fasting venous blood was drawn in the morning after at least 30 minutes of rest in supine position. BNP levels were measured using the RIA method (SHIONORIA-BNP, CIS Bio International).

Statistical analysis

The values are given as a mean ± standard deviation. The Mann-Whitney and χ^2 tests were used to evaluate the significance of differences between groups. Because BNP values were not normally distributed, natural logarithmic transformation was used for statistical analysis when needed. Correlations between variables were assessed using Spearman rank test. Logistic regression analysis was used to assess which variables were independently correlated with RFP and PHT. A p value <0.05 was taken to be statistically significant. All analyses were performed using the Statistica 7.0 package.

Results

Patients' characteristics are summarised in Table I. There were 26 patients with RFP and 30 with a non-restrictive filling pattern (the non-RFP group). There were no significant differences in age, gender, NYHA class (p=0.06), heart rate at rest (p=0.09), ischaemic cardiomyopathy prevalence or medical treatment between the two groups.

According to the echocardiographic findings, there were no significant differences in LV systolic and diastolic diameters, left atrial (LA) diameter or LVEF between the groups (Table II). The RFP patients had increased right ventricular diameter (RVEDD) and PASP compared to the non-RFP group. Also, PHT prevalence was significantly higher in the RFP patients (65 vs. 20%; p=0.0006).

The patients with RFP showed higher levels of BNP (p=0.003) than the non-RFP patients. They also exhibited more impaired exercise capacity, with lower peak VO_2 and higher VE/VCO_2 slope. The prevalence of enhanced ventilatory response to exercise (VE/VCO_2 slope ≥35) was significantly higher in patients with RFP than non-RFP subjects (61.5 vs. 27%; p=0.009).

Table I. Clinical characteristics of patients with restrictive (RFP) and non-restrictive (non-RFP) filling pattern

Parameter	RFP group (n=26)	non-RFP group (n=30)	p
Age [years]	50.5±10.5	52.3±9.3	NS
NYHA class	2.7±0.8	2.3±0.8	0.06
Heart rate at rest [1/min]	80.7±10.2	77.1±12.3	0.09
Ischaemic cardiomyopathy [%]	50	53	NS
ACE inhibitors [%]	85	100	NS
Beta-blockers [%]	77	70	NS
Digoxin [%]	50	50	NS
Furosemide [%]	88	77	NS
BNP [pg/ml]	90.6±65.9	50.4±60.7	0.003

Table II. Echocardiographic and functional characteristics of patients with RFP and non-RFP

Parameter	RFP group (n=26)	non-RFP group (n=30)	p
LVEF [%]	25.5±6.8	26.6±8	NS
LVEDD [mm]	72.2±9.3	71.3±8.2	NS
LVESD [mm]	63.7±9.4	61.3±8.7	NS
LA [mm]	49.9±6.4	46.4±6.3	NS
RVEDD [mm]	34.9±8.0	29.9±4	0.01
PASP [mmHg]	49.3±13.8	37.2±12.6	0.02
E [cm/s]	96.1±17.9	64.4±21.3	<0.0001
DTE [ms]	102.9±21.3	212±56	<0.0001
A [cm/s]	40.7±16.1	81.1±14.6	<0.0001
E/A	2.7±1.1	0.82±0.3	<0.0001
Mitral regurgitation [grade]	2.6±0.9	1.9±1.0	0.004
Peak VO_2 [ml/kg/min]	15.4±4.1	17.8±4.9	0.046
VE/VCO_2 slope	36.3±5.9	31.9±6.3	0.01

Abbreviations: see 'Methods' section

Table III. Correlations between DTE and evaluated parameters

	LVEF	NYHA	BNP	Peak VO_2	VE/VCO_2 slope	PASP
r	0.19	–0.24	–0.48	0.29	–0.35	–0.39
p	NS	NS	0.0002	0.03	0.01	0.03

Abbreviations: r – correlation coefficient

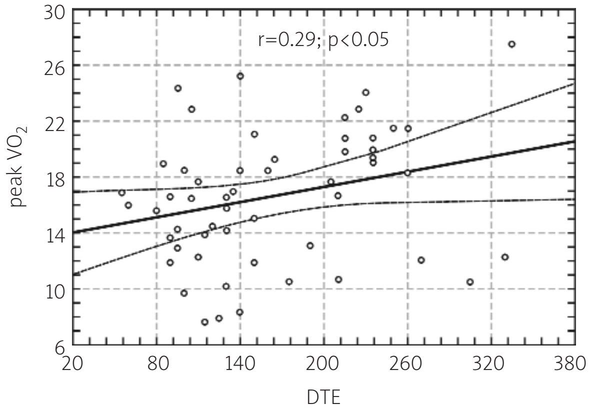

Figure 1. Correlation between DTE and peak VO_2

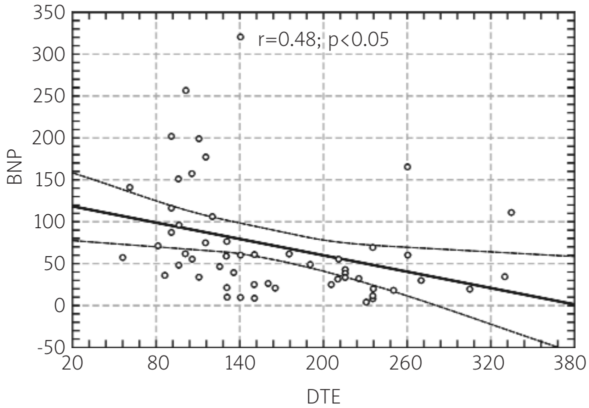

Figure 2. Correlation between DTE and BNP levels

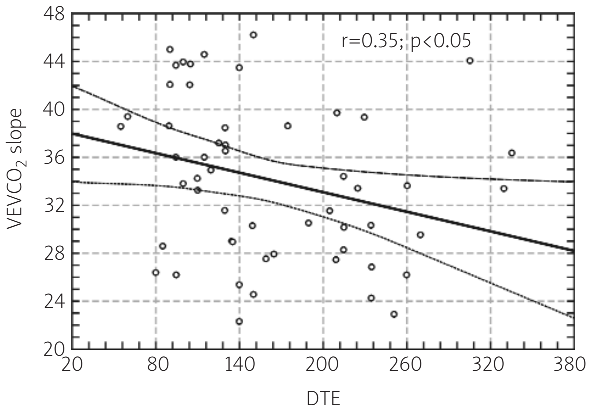

Figure 3. Correlation between DTE and VE/VCO_2 slope

According to the diastolic function parameters, a significant correlation between DTE and peak VO_2 (r=0.29; p=0.03) (Figure 1), and inverse correlations between DTE and BNP levels (r=–048; p=0.0002) (Figure 2), or VE/VCO_2 slope (r=–0.35; p=0.01) (Figure 3) were found (Table III). There was also a trend towards

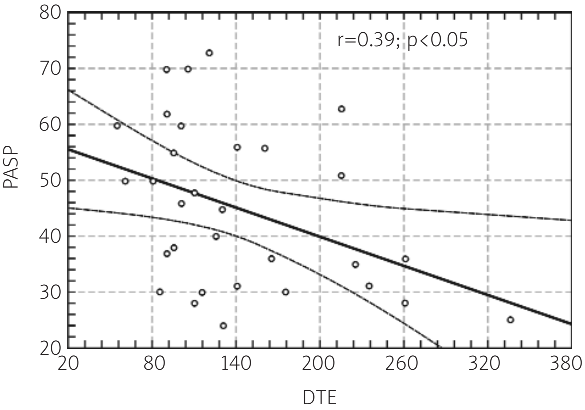

Figure 4. Correlation between DTE and PASP

a correlation between the E/A ratio and BNP levels (r=0.36; p=0.07). Logistic regression analysis performed with inclusion of logarithmically transformed BNP, peak VO_2, and VE/VCO_2 slope showed that only BNP (Wilk's Lambda=0.882; p=0.049) was an independent variable for predicting RFP.

In the investigated group, 23 patients had PHT. Patients with PHT had higher BNP levels (92.2±68.6 vs. 52.9±59.6 pg/ml; p=0.01) and prevalence of RFP (74 vs. 27%; p=0.0006) in comparison to patients without PHT. There were no significant differences in peak VO_2, VE/VCO_2 slope or LVEF. There were significant correlations between PASP and diastolic function parameters: E/A (r=0.49; p=0.005), E (r=0.47; p=0.007), DTE (r=–0.39; p=0.03) (Figure 4), and A (r=–0.44; p=0.01). There were no significant correlations between PASP and LVEF, BNP levels, peak VO_2 or VE/VCO_2 slope. Logistic regression analysis revealed that among BNP, peak VO_2, VE/VCO_2 slope and RFP, the only independent variable for predicting PHT was RFP (OR 0.131; 95% CI 0.033-0.528; p=0.005).

Discussion

We have shown that RFP is an independent predictor of PHT. Furthermore, RFP is associated with higher levels of BNP, lower peak VO_2 and higher VE/VCO_2 slope, indicating that this pattern is associated with severe HF.

Recently, the pathophysiology and clinical importance of the transmitral flow velocity pattern as assessed by Doppler echocardiography has been extensively investigated [1, 2, 7, 11]. It has been shown that RFP can predict LV pressures with high specificity and sensitivity in patients with systolic dysfunction [11, 12]. Severe diastolic dysfunction is associated with more severe symptoms, decrease in exercise capacity and adverse prognosis [1-4].

Our study extends previous observations that in patients with systolic HF, RFP is associated with reduced peak VO_2 [2, 3], while an association was also found between RFP and VE/VCO_2 slope. High VE/VCO_2 slope is a marker of excessive exercise ventilation in patients with HF and is an important prognostic factor, even better than peak VO_2 [13, 14]. Patients with RFP had significantly higher VE/VCO_2 slope than patients with non-RFP and the prevalence of those with enhanced ventilatory response to exercise (VE/VCO_2 slope ≥35) was significantly higher in the group with RFP than non-RFP. There was also a significant correlation between DTE and VE/VCO_2 slope. To our knowledge there are no published data on the relationship between LV diastolic dysfunction and ventilatory response to exercise.

In HF, BNP is secreted by ventricular myocardial cells in response to high ventricular filling pressures [15]. It has been suggested that stretch of cardiomyocytes is the most important stimulus of BNP secretion. It is also believed that BNP in the clinical setting may be released from the heart in response to increased wall stress [16]. In our study, BNP levels were significantly higher in patients with RFP in comparison to the non-RFP patients, and BNP was the only independent predictor of RFP. These findings are in agreement with previous studies showing that in systolic HF, BNP levels are related to diastolic function, as assessed using transmitral flow parameters and newer indices measured from tissue Doppler imaging and color M-mode [7, 17]. Additionally, Lubien et al. [18] reported that BNP can reliably detect the presence of diastolic dysfunction in echocardiography even in patients with normal systolic function. Yu et al. [7] found, similar to our findings, that RFP was associated with higher BNP levels, higher pulmonary artery systolic pressure and, contrary to our findings, with lower LVEF. However, their patients were older than ours and they did not perform a cardiopulmonary exercise test to assess functional capacity. Recently, Patrianakos et al. [3] found that natriuretic peptides Nt-ANP and Nt-BNP are excellent markers of diastolic dysfunction in patients with HF. They also showed that the strongest independent predictors for RFP in patients with non-ischaemic dilated cardiomyopathy were Nt-ANP and IL-6, while Nt-BNP levels were the strongest peak VO_2 predictors.

In our study, pulmonary arterial systolic pressure and prevalence of PHT were significantly higher in patients with RFP than in the non-RFP subjects. We found a significant correlation between PASP and parameters of LV diastolic function. Logistic regression analysis revealed that only RFP was an independent predictor of PHT. Pulmonary hypertension is a frequent finding in patients with systolic HF and is an important predictive marker of early mortality after orthotopic transplantation [19]. Recently, the determinants and clinical importance of PHT have been extensively investigated [9, 10]. Enriquez-Sarano et al. [9], who investigated echocardiographic determinants of PHT in patients with LV systolic dysfunction, found that LV diastolic function (shorter DTE) and degree of mitral regurgitation were independent predictors of PASP, whereas LVEF was not an independent predictor of PASP. In agreement with these findings, Capomolla et al. [10] found that the degree of diastolic dysfunction strongly correlated with systolic PHT, whereas, contrary to Enriquez-Sarano et al. [9], mitral regurgitation was not significantly related to PASP. In their study noninvasive determinants had predictive power similar to that of invasive determinants of PHT.

Diastolic LV function is a complex phenomenon and RFP, which is diagnosed based on short deceleration time of mitral E wave and increased E/A ratio, is the most severe degree of diastolic dysfunction [20]. Short deceleration time is associated with high diastolic LV pressure and reduced global atrial and ventricular compliance. In PHT, shortened DTE may be attributable to the right ventricular (RV) pressure overload, which causes geometrical changes such as abnormal ventricular septal motion [21]. The investigators mentioned above did not assess BNP levels and exercise capacity. In our study patients with PHT had significantly higher BNP levels in comparison to patients without PHT. Some recently published papers evaluated the role of BNP in detection of PHT in patients with respiratory disease [22]. It has been shown that in patients with PHT and isolated RV overload, BNP levels are increased in proportion to the extent of RV dysfunction [23].

Peak VO_2 is an established marker of HF severity, but it is not clear whether exercise capacity may differentiate patients with PHT from those without PHT. In patients with lung fibrosis, exercise capacity was reduced in patients with PHT in comparison to patients with no PHT as assessed using 6-MWT [23]. Comparison of cardiopulmonary exercise test results in patients with HF and in patients with PHT revealed that the test profile differs by showing similarly reduced peak VO_2 but more dyspnoea at a comparable level of exercise in patients with PHT [24]. Contrary to Kruger et al. [25], there were not significant differences in exercise capacity (peak VO_2) and exercise ventilation (VE/VCO_2 slope) between patients with and without PHT in our study.

Conclusions

Severe LV diastolic dysfunction in patients with systolic HF is an independent predictor of PHT. Furthermore, it is associated with increased BNP levels and decreased exercise capacity.

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Restrykcyjny model napływu mitralnego jest wskaźnikiem nadciśnienia płucnego, podwyższonego poziomu BNP i upośledzonej tolerancji wysiłkowej w niewydolności serca

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Streszczenie

Wstęp: U chorych ze skurczową niewydolnością serca (HF) często występuje dysfunkcja rozkurczowa lewej komory serca. Ciężka jej forma, w postaci restrykcyjnego charakteru napływu mitralnego (RFP), jest wskaźnikiem obniżonej tolerancji wysiłku i złego rokowania u takich chorych. Podwyższone w HF stężenia peptydów natriuretycznych są również wskaźnikami obniżonej tolerancji wysiłku i rokowniczymi. Częstym, rokowniczo niekorzystnym zjawiskiem w HF jest nadciśnienie płucne. Wydaje się, że dobrym wskaźnikiem wysokości ciśnienia płucnego w skurczowej HF są parametry czynności rozkurczowej lewej komory.

Cel: Zbadanie zależności pomiędzy restrykcyjnym modelem napływu mitralnego a stężeniem peptydu natiuretycznego typu B (BNP), obecnością nadciśnienia płucnego i tolerancją wysiłku u chorych ze stabilną klinicznie skurczową niewydolnością serca.

Metodyka: U 56 chorych z niewydolnością serca i niską frakcją wyrzutową lewej komory (LVEF) wykonano standardowe badanie echokardiograficzne i maksymalny test wysiłkowy na bieżni ruchomej z analizą gazów wydechowych. Restrykcyjny charakter napływu mitralnego rozpoznawano, gdy E/A ≥2 lub 1< E/A <2, z czasem deceleracji fali E (DTE) ≤130 ms. Skurczowe ciśnienie płucne (PASP) obliczano jako największy gradient ciśnień przez zastawkę trójdzielną plus 10. Nadciśnienie płucne (PHT) definiowano jako PASP ≥35 mmHg. Tolerancję wysiłku oceniano jako peak VO_2, a VE/VCO_2 slope stanowił wskaźnik wentylacji wysiłkowej. Stężenie BNP badano metodą RIA.

Wyniki: Średni wiek badanych wynosił 51,4±9,9 roku, LVEF – 26,1±7%. Wszyscy mieli rytm zatokowy. Restrykcyjny profil napływu mitralnego rozpoznano u 26 chorych (grupa I), nierestrykcyjny (grupa II) – u 30. Grupy nie różniły się istotnie pod względem wieku, płci, klasy NYHA, częstotliwości serca w spoczynku, występowania kardiomiopatii niedokrwiennej i stosowanego leczenia. W badaniu echokardiograficznym nie było istotnych różnic w wymiarze końcowoskurczowym i końoworozkurczowym lewej komory, wielkości lewego przedsionka i LVEF. W grupie I w porównaniu z II stwierdzono istotnie większe stężenie BNP (90,6±66 *vs* 50,4±61 pg/ml; p=0,003), istotnie mniejszy peak VO_2 (15,4±4,1 *vs* 17,8±4,9 ml/kg/min; p=0,046) oraz istotnie większe VE/VCO_2 slope (36,3±5,9 *vs* 31,9±6,3; p=0,01) i PASP (49,3±13,8 *vs* 37,2±12,6 mmHg; p=0,02). Stwierdzenie powiązań pomiędzy nasileniem wentylacji wysiłkowej (VE/VCO_2 slope) a restrykcją jest obserwacją nową. Nadciśnienie płucne występowało istotnie częściej w grupie z restrykcją niż bez restrykcji (65 *vs* 20%; p=0,0006). Stwierdzono istotne korelacje pomiędzy wskaźnikiem czynności rozkurczowej lewej komory (DTE) a peak VO_2 (r=0,28; p=0,02) oraz ujemne korelacje DTE ze stężeniami BNP (r=–0,48; p=0,003), VE/VCO_2 slope (r=–0,28; p=0,02) i PASP (r=–0,46; p=0,003). Istotne były również korelacje pomiędzy E/A a stężeniami BNP (r=0,36; p=0,07) i PASP (r=0,49; p=0,005). W badanej grupie 23 chorych miało nadciśnienie płucne. Chorzy z PHT w porównaniu z chorymi bez PHT mieli istotnie większe stężenie BNP. W analizie regresji logistycznej z uwzględnieniem stężenia BNP, peak VO_2, VE/VCO_2 slope i obecności restrykcji (RFP), tylko RFP była niezależnym wskaźnikiem nadciśnienia płucnego.

Wnioski: Restrykcyjny profil napełniania lewej komory serca jest wskaźnikiem nadciśnienia płucnego u chorych ze skurczową niewydolnością serca i jest związany ze zwiększonym stężeniem BNP oraz gorszym wynikiem sercowo-płucnego testu wysiłkowego.

Słowa kluczowe: niewydolność serca, dysfunkcja rozkurczowa, BNP, nadciśnienie płucne, test spiroergometryczny

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