

# Analysis of correlations between N-terminal pro-B-type natriuretic peptide levels and markers of venous pulmonary hypertension in patients referred for heart transplantation

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## KEY WORDS

heart failure, heart transplantation, NT-proBNP, secondary venous pulmonary hypertension

## ABSTRACT

**INTRODUCTION** Heart failure (HF) is a growing health care problem in the world. Secondary pulmonary venous hypertension is usually observed in patients with end-stage heart failure.

**OBJECTIVES** The main purpose of the study was to evaluate the relationships between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the markers of secondary venous pulmonary hypertension in patients referred for heart transplantation (HTX).

**PATIENTS AND METHODS** This retrospective analysis included 35 patients (32 men, 3 women; median age, 55.0; interquartile range [IQR] 12.0 years). The study group consisted of all consecutive patients referred for HTX, in whom the right-heart catheterization using the Swan-Ganz catheter was performed at the same time as the measurement of NT-proBNP levels.

**RESULTS** A high median value of NT-proBNP (3187.0; IQR 2964.0 pg/ml) and elevated pulmonary pressure were observed in the study group. There was a significant correlation between NT-proBNP levels and the values of systolic, mean, and diastolic pulmonary artery pressure ( $r = 0.5$ ,  $P = 0.001$ ;  $r = 0.5$ ,  $P = 0.001$ ;  $r = 0.5$ ,  $P = 0.002$ ; respectively) as well as cardiac output ( $r = -0.4$ ,  $P = 0.007$ ). There was also a positive correlation between pulmonary artery resistance and NT-proBNP levels ( $r = 0.5$ ,  $P = 0.006$ ).

**CONCLUSIONS** In our study population, the median value of NT-proBNP levels exceeded the normal range 25 times. There was a correlation between the markers of secondary pulmonary hypertension and cardiac output and NT-proBNP levels. Elevated NT-proBNP levels in patients with end-stage HF may be associated with significant secondary venous pulmonary hypertension.

**INTRODUCTION** Chronic heart failure (HF) has been recently described as a growing pandemic. In developed countries, HF affects about 2% of the general population. What is worse, about 10% of the patients have advanced HF, which is associated with 1-year mortality of 50%.<sup>1</sup>

In patients scheduled for heart transplantation (HTX), ischemic cardiomyopathy and congestive

cardiomyopathy are the most often causes of end-stage HF.<sup>2</sup> In both conditions, end-stage left ventricular failure leads to stasis of antegrade blood flow (in relation to mitral valve), which in turn leads to secondary venous pulmonary hypertension. Pulmonary hypertension with high pulmonary arterial resistance (usually above 6 Wood units) makes HTX impossible or extremely

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**TABLE 1** Patient characteristics

number of patients		35
sex, n (%)	male	32 (91.4)
	female	3 (8.6)
age, y		55.0 (12.0)
BSA, m <sup>2</sup>		1.96 ± 0.2
etiology of cardiomyopathy, n (%)	congestive	10 (28.6)
	ischemic	25 (71.4)
previous surgery, n (%)		3 (8.6)
AF, n (%)		7 (20)
creatinine, μmol/l		99.4 ± 24.4
risk factor(s) for ischemic disease, n (%)		25 (71.4)
hemoglobin, g/dl		13.9 ± 1.9
LVED, cm		7.3 ± 0.7
LVEF, %		16.0 ± 4.5

Data are presented as number (percentage), mean ± standard deviation or median and interquartile range.

Abbreviations: AF – atrial fibrillation, BSA – body surface area, LVED – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction

risky.<sup>3,4</sup> B-type natriuretic peptide (BNP) belongs to the natriuretic peptide family. These polypeptide neurohormones participate in the regulation of water and sodium and cardiovascular homeostasis. Natriuretic peptides are well-known markers of cardiac etiology of dyspnea.<sup>5</sup>

In the literature, there are numerous reports concerning the correlation between BNP levels or N-terminal pro-BNP (NT-proBNP) and the presence of arterial pulmonary hypertension (primary or secondary to systemic shunts) or thromboembolic pulmonary hypertension. However, there is scarce data relating to the interdependence between BNP (or NT-proBNP) levels and secondary venous pulmonary hypertension in patients scheduled for HTX.

The purpose of the study was to assess the relationship between NT-proBNP levels and secondary venous pulmonary hypertension in patients referred for HTX.

**PATIENTS AND METHODS** This retrospective analysis of medical records was approved by the Institutional Board Review. The study group consisted of 35 patients consecutively referred for HTX (32 men, 3 women; median age, 55.0, interquartile range [IQR] 12.0 years). Twenty-five patients had ischemic and 10 patients had congestive cardiomyopathy. NT-proBNP levels were determined in the years 2010 and 2011 (the method of BNP measurement was changed in 2010). Echocardiography revealed significant enlargement of the left ventricular end-diastolic dimension (LVED; mean, 7 cm) and severely diminished left ventricular ejection fraction (LVEF; mean, 15%). Mean hemoglobin levels were in the low normal range and mean creatinine levels were below 99 μmol/l (only 1 patient had creatinine >140 μmol/l). All patients received tailored pharmacotherapy according to the guidelines.

The standard treatment consisted of β-blockers (mainly carvedilol), angiotensin-converting enzyme inhibitors, diuretics (spironolactone, loop diuretics such as furosemide and torasemide). Patients with ischemic cardiomyopathy were additionally given acetylsalicylic acid. Detailed characteristics of the patients are presented in **TABLE 1**.

The inclusion criteria (35 patients) were as follows: planned HTX, measurement of NT-proBNP levels with the same method, right-heart catheterization (with pulmonary hypertension assessment) performed at the time of NT-proBNP measurement. The exclusion criteria were as follows (2 patients): unreliable right-heart catheterization measurements (in the opinion of the investigators).

NT-proBNP levels were measured in blood plasma with the chemiluminescence method (COBAS apparatus, ROCHE, Japan); the levels below 125 pg/ml were considered as within the normal range. Right-heart catheterization was performed at the same time as NT-proBNP measurement (during the same hospital stay) using the Swan-Ganz catheter. Indicators of pulmonary artery pressure (PAP), including systolic PAP (SPAP), diastolic PAP (DPAP), and mean PAP (MPAP), as well as pulmonary artery resistance (PAR) were measured and calculated. Cardiac output (CO) was calculated using the Fick formula. PAR was calculated using the formula:  $PAR = DPAP - PCWP/CO$ , where PCWP = pulmonary capillary wedge pressure. The cardiac index (CI) was calculated using the formula:  $CI = CO/BSA$ , where BSA = body surface area.

The normal ranges of the parameters measured and calculated during right-heart catheterization are presented in **TABLE 2**.<sup>6</sup>

The reversibility of pulmonary hypertension was assessed when PAR was above 320 dynes × s/cm<sup>5</sup> (according to our original protocol implemented in 2000).<sup>7</sup> NT-proBNP levels were correlated with baseline hemodynamic parameters.

A statistical analysis was performed using STATISTICA 8.0. The Shapiro-Wilk test was used to test for a normal distribution. Normally distributed data were expressed as the arithmetic mean with standard deviation. Nonnormally distributed data were expressed as median and interquartile range (IQR). The Pearson *r* test was used

**TABLE 2** Normal range of parameters measured during right-heart catheterization

SPAP, mmHg	15–30
DPAP, mmHg	4–12
MPAP, mmHg	9–18
PAR, dynes s/cm <sup>5</sup>	<160
CO, l/min	4–8
CI, l/min/m <sup>2</sup>	2.4–4.0

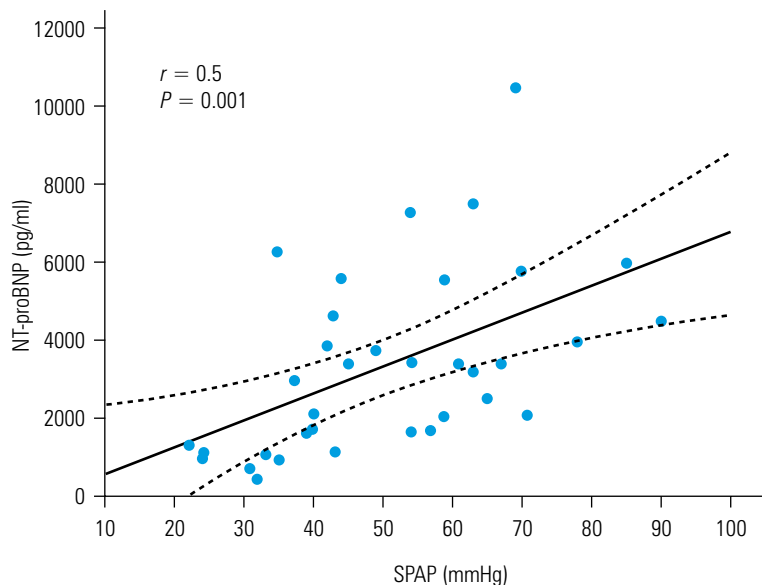
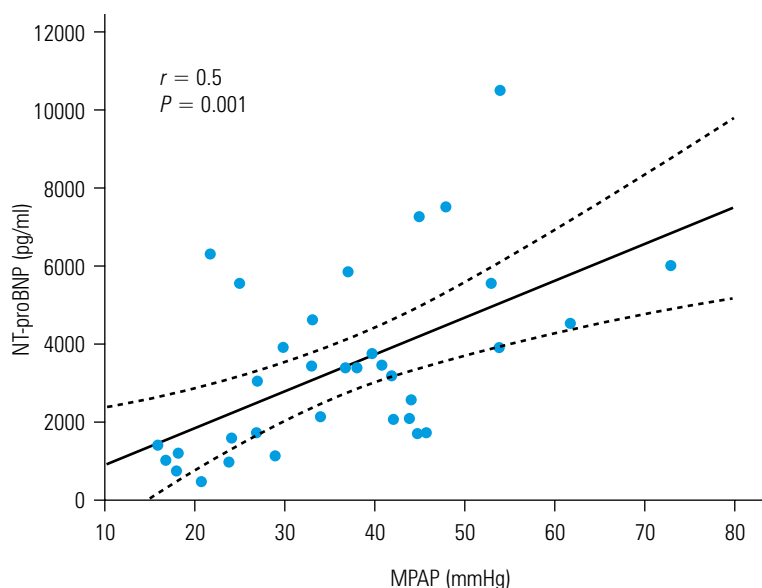
Abbreviations: CI – cardiac index, CO – cardiac output, DPAP – diastolic pulmonary artery pressure, MPAP – mean pulmonary artery pressure, PAR – pulmonary artery resistance, SPAP – systolic pulmonary artery pressure

**TABLE 3** Pulmonary artery pressure in the study group

Pulmonary pressure	Value
SPAP, mmHg	50.8 ± 17.4
DPAP, mmHg	27.9 ± 11.3
MPAP, mmHg	36.3 ± 13.5

Data are presented as mean ± standard deviation.

Abbreviations: see TABLE 2

**FIGURE 1** Correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and systolic pulmonary artery pressure (SPAP)**FIGURE 2** Correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and mean pulmonary artery pressure (MPAP)

to study the relationships between 2 values. Statistical significance was considered as  $P$  less than 0.05. A multivariate regression was performed to assess the significance of parameters.

**RESULTS** A high median value of NT-proBNP was observed in the study group (3187.0; IQR, 2964.0 pg/ml). We also noted elevated pulmonary pressure with SPAP above 50 mmHg (mean value) (TABLE 3). The analysis of hemodynamic parameters showed low CO and CI values (median CO, 3.7; IQR, 1.4 l/min; CI, 1.8; IQR, 0.7 l/min/m<sup>2</sup>; respectively). PAR was also significantly elevated (median PAR, 250.9; IQR, 248.3 dynes × s/cm<sup>5</sup>).

In the study group, 12 patients received vasodilators (nitroglycerine or nitric oxide). The reversibility test was not performed in 2 patients for clinical reasons. The reversibility of pulmonary hypertension (i.e., a decrease in PAR below 320 dynes × s/cm<sup>5</sup>) was observed in 10 patients. Only 2 patients had persistent pulmonary hypertension (BNP, 5935 pg/ml and 2044 pg/ml, respectively). Because of a small sample size (2 patients), statistical analysis was not performed.

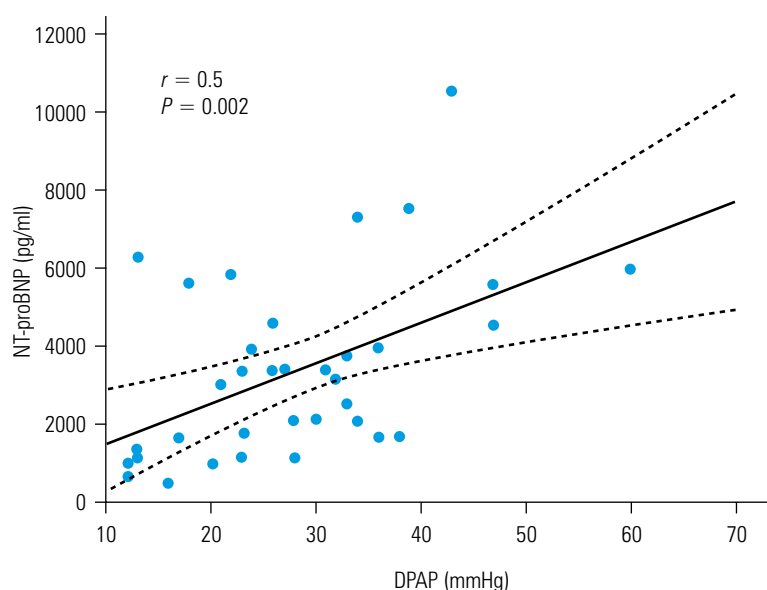
A significant correlation was observed between NT-proBNP levels and SPAP, MPAP, and DPAP ( $r = 0.5$ ,  $P = 0.001$ , FIGURE 1;  $r = 0.5$ ,  $P = 0.001$ , FIGURE 2;  $r = 0.5$ ,  $P = 0.002$ , FIGURE 3; respectively). Similarly, there was a significant correlation between CO and NT-proBNP levels ( $r = -0.4$ ,  $P = 0.007$ , FIGURE 4). However, there was no statistical correlation between CI and NT-proBNP levels ( $r = -0.3$ ,  $P = 0.07$ , FIGURE 5). Finally, we found a significant correlation between PAR and NT-proBNP levels ( $r = 0.5$ ,  $P = 0.006$ , FIGURE 6).

A multivariate regression analysis showed that none of the parameters assessed during right-heart catheterization, i.e., SPAP, DPAP, MPAP, CO, CI, PAR, was an independent predictor of NT-proBNP levels ( $P = 0.45$ ;  $P = 0.23$ ;  $P = 0.18$ ;  $P = 0.12$ ;  $P = 0.32$ ;  $P = 0.61$ ; respectively). However, a more general multiple regression model revealed a significant effect of the above parameters on NT-proBNP levels ( $R = 0.63$ ; adjusted  $R^2 = 0.27$ ;  $P = 0.017$ ).

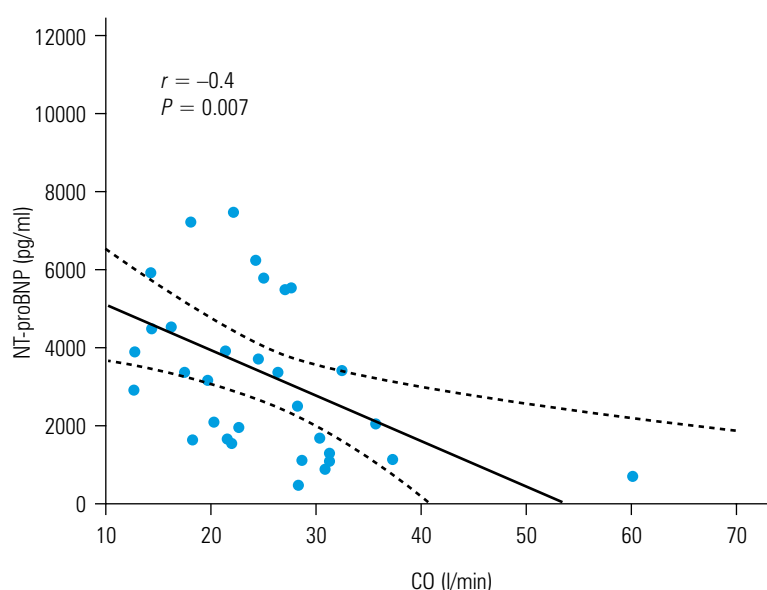
There was no correlation between patients' age and the LVED or LVEF ( $r = 0.01$ ,  $P = 0.94$ ;  $r = -0.1$ ,  $P = 0.95$ ;  $r = -0.1$ ,  $P = 0.45$ ; respectively). Neither the LVED nor LVEF correlated with NT-proBNP levels.

In the follow-up period (i.e., since 2010 – present), 6 patients underwent HTX, 11 patients remain on the active waiting list, 14 patients were not eligible for HTX, and 4 patients died.

**DISCUSSION** BNP is a recognized marker of systolic and diastolic HF.<sup>5,8</sup> BNP measurement has become an important tool for establishing a reliable diagnosis, predicting prognosis, and guiding medical therapy.<sup>9</sup> It has also proved to be clinically useful in a wide spectrum of other cardiovascular disorders. It has a valuable prognostic significance in patients undergoing permanent pacemaker implantation.<sup>10</sup> Serum BNP levels have also been associated with cardioembolic stroke, as well as functional outcome and mortality after ischemic stroke.<sup>11</sup>



**FIGURE 3** Correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and diastolic pulmonary artery pressure (DPAP)



**FIGURE 4** Correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and cardiac output (CO)

According to the International Society for Heart and Lung Transplantation (ISHLT) guidelines, right-heart catheterization is one of the mandatory tests and should be performed in all candidates for HTX (class I, level of evidence C). Right-heart catheterization should be scheduled at baseline evaluation and then repeated at an interval of 3 to 6 months in potential candidates for HTX (class I, level of evidence C). Hemodynamic reassessment is advisable especially in the presence of reversible pulmonary hypertension or worsening of HF symptoms (class I, level of evidence C).

Detailed assessment of the markers of pulmonary hypertension is crucial in therapeutic decision making, because this pathology is considered a contraindication to HTX (when PAR is more than 5 Wood units, or the PAR index is above 6,

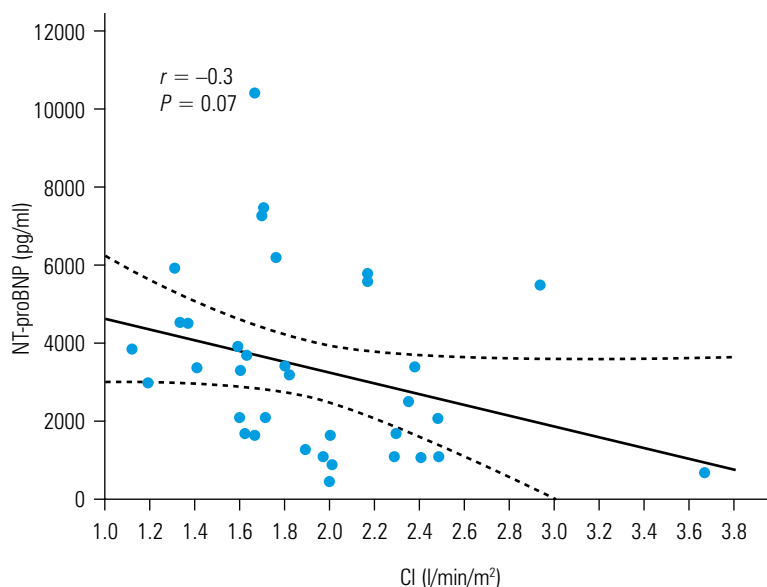
or the transpulmonary gradient exceeds 16 to 20 mmHg). Significant pulmonary hypertension (SPAP above 60 mmHg with any of the 3 preceding variables) increases the risk of right HF and early death after HTX. If PAR can be reduced to less than 2.5 with a vasodilator but the systolic blood pressure falls below 85 mmHg, the patient remains at high risk of right HF and mortality after HTX.<sup>4,12</sup>

Previous studies have shown the clinical utility of BNP (and NT-proBNP) in pulmonary artery hypertension. Leuchte et al.<sup>13</sup> suggested a close relationship between plasma BNP levels and functional impairment in patients with primary pulmonary hypertension. BNP levels paralleled the extent of pulmonary hemodynamic changes and right HF.<sup>13</sup> Nagaya et al.<sup>14</sup> investigated the effect of right ventricular (RV) hemodynamic variables on the secretion of BNP in 44 patients with isolated RV overload (due to atrial septal defect, primary or thromboembolic pulmonary hypertension). They found a strong relationship between plasma BNP levels and the extent of RV dysfunction in pulmonary hypertension. Plasma BNP correlated positively with MPAP, total PAR, mean right atrial pressure, RV end-diastolic pressure, and RV myocardial mass. Mauritz et al.<sup>15</sup> studied the value of serial NT-proBNP measurements in patients with arterial pulmonary hypertension. The authors examined 198 patients. Serial measurements allowed for the calculation of baseline NT-proBNP, providing an excellent discrimination between survivors and nonsurvivors with the cut-off value of 1.256 pg/ml or higher. Moreover, Andreassen et al.<sup>19</sup> demonstrated that plasma NT-proBNP can be used to determine the clinical severity of the disease and is associated with long-term mortality, in a heterogeneous group of patients with chronic precapillary pulmonary hypertension.<sup>16</sup> There are several reports concerning the clinical weight of plasma BNP concentration in the management of pulmonary arterial hypertension. Park et al.<sup>17</sup> established the utility of BNP for predicting response to epoprostenol therapy in pulmonary artery hypertension.

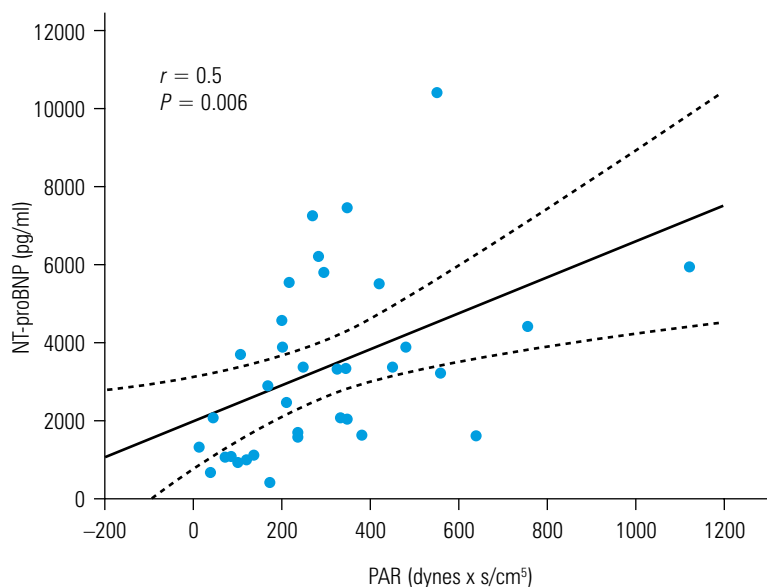
There is only one study concerning BNP as a predictor of severe pulmonary hypertension in candidates for HTX. Kubanek et al.<sup>18</sup> examined the population of 43 patients scheduled for HTX. All patients underwent repeat right-heart catheterizations (at 3 to 4 month intervals) and blood sampling for BNP and big-endothelin-1 analysis. Serial BNP testing allowed for reliable detection of the development of severe pulmonary hypertension.

Our study supports these findings. We observed a high median value of NT-proBNP (3187.0; IQR, 2964.0 pg/ml) in 35 patients referred for HTX. NT-proBNP levels significantly correlated with the values of systolic, mean, and diastolic pulmonary artery pressures, as well as with pulmonary arterial resistance.

According to the ISHLT guidelines, the patient awaiting HTX should be re-evaluated



**FIGURE 5** Correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and cardiac index (CI)



**FIGURE 6** Correlation between N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and pulmonary artery resistance (PAR)

with right-heart catheterization at every 3 to 6 months. However, the clinical data may suggest even more frequent hemodynamic assessment, and right-heart catheterization remains an invasive procedure with potential complications. We are still looking for an ideal, noninvasive test providing a reliable diagnosis of pulmonary hypertension.

Echocardiography has been used to estimate SPAP, based on the measurements of tricuspid regurgitant (TR) jet velocity. This method has been shown to be highly accurate compared with invasive measurements over a wide range of values. However, this approach requires the presence of tricuspid regurgitation, obtaining a parallel intercept angle between the TR jet and the ultrasound beam, as well as a complete the spectrum of TR

continuous wave curve (the most common limitation). There have been some reports suggesting severe left ventricular diastolic dysfunction as an independent predictor of pulmonary hypertension. Straburzyńska-Migaj et al.<sup>20</sup> found a correlation between restrictive filling pattern, increased BNP levels, worse results of cardiopulmonary exercise test, and pulmonary hypertension.

Considering the above data, right-heart catheterization is the gold standard in diagnosing pulmonary hypertension.

The results of our study suggest that serial NT-proBNP measurements should be regarded as the standard assessment in candidates for HTX. The analysis of NT-proBNP levels may identify patients at higher risk of severe secondary venous pulmonary hypertension. A significant NT-proBNP elevation in comparison with the baseline levels should hasten repeat right-heart catheterization even if long before the time-limit recommended by the guidelines.

**Study limitations** A retrospective analysis and limited sample size due to altered methodology of NT-proBNP measurement should be considered the major limitation of the present study.

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# Ocena zależności pomiędzy poziomem N-końcowego propeptydu natriuretycznego typu B a wskaźnikami żylnego nadciśnienia płucnego u chorych kwalifikowanych do przeszczepienia serca

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## SŁOWA KLUCZOWE

niewydolność serca,  
NT-proBNP, przeszczep  
serca, żylne  
nadciśnienie płucne

## STRESZCZENIE

**WPROWADZENIE** Niewydolność serca stanowi rosnący problem zdrowotny na świecie. W krańcowej niewydolności serca często obserwuje się wtórne żylne nadciśnienie płucne.

**CELE** Głównym celem pracy było określenie zależności między poziomem N-końcowego propeptydu natriuretycznego typu B (NT-proBNP) a markerami wtórnego żylnego nadciśnienia płucnego wśród pacjentów kwalifikowanych do przeszczepienia serca (*heart transplantation* – HTX).

**PACJENCI I METODY** Retrospektywną analizą objęto 35 pacjentów (32 mężczyzn oraz 3 kobiety; mediana wieku 55,0; przedział międzykwartylowy (PK) 12,0 lat). Grupę badaną stanowili wszyscy kolejni pacjenci kwalifikowani do HTX, u których wykonano cewnikowanie prawostronne serca za pomocą cewnika Swana i Ganza w okresie oceny poziomu NT-proBNP.

**WYNIKI** W badanej grupie zaobserwowano wysoką medianę NT-proBNP (3187,0; PK 2964,0 pg/ml) oraz podwyższone ciśnienie w tętnicy płucnej. Stwierdzono istotną zależność między poziomem NT-proBNP a skurczowym, średnim i rozkurczowym ciśnieniem w tętnicy płucnej (odpowiednio:  $r = 0,5$ ;  $p = 0,001$ ;  $r = 0,5$ ;  $p = 0,001$ ;  $r = 0,5$ ;  $p = 0,002$ ), a także rzutem serca ( $r = -0,4$ ;  $p = 0,007$ ). Stwierdzono dodatnią korelację pomiędzy oporem w tętnicach płucnych a poziomem NT-proBNP ( $r = 0,5$ ;  $p = 0,006$ ).

**WNIOSKI** W badanej populacji mediana poziomu NT-proBNP przekraczała normę średnio 25 razy. Stwierdzono korelację między parametrami wtórnego żylnego nadciśnienia płucnego i rzutem serca a poziomem NT-proBNP. Podwyższony poziom NT-proBNP u chorych z krańcową niewydolnością serca może świadczyć o obecności istotnego wtórnego żylnego nadciśnienia płucnego.

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