INTRODUCTION

Aortic stenosis (AS), usually of degenerative etiology, is the most common form of valvular heart disease. Aortic valve replacement is explicitly recommended in severe, symptomatic AS with preserved left ventricular ejection fraction (LVEF). However, in elderly patients, breathlessness and chest tightness may be recognized as nonspecific symptoms secondary to diminished physical fitness. Another important issue are comorbidities, which are common in the elderly, are related to the general condition of the patient, and are determinants of the operative risk. Ultimately, the decision to operate is based on a delicate balance between the risk and the outcome benefit of aortic valve replacement. The identification of patients with the most severe
AS exhibiting its hemodynamic effects on cardiac function and understanding the pathophysiology of cardiac deterioration may help in decision making before a surgical or, alternatively, transcutaneous intervention. Although echocardiography remains the main examining tool in valvular disease and heart failure, neurohormones, adipokines, and several extracellular matrix modulators have been recently assessed as potential pathogenetic, diagnostic, and prognostic factors in AS. In some patients presenting with small aortic valve area (AVA), a “low-flow” (LF) condition may be present, defined as a reduced stroke volume index (SVI) lower than 35 ml/m². Of interest, even in the population with a high mean gradient (HMG >40 mmHg), some patients may present with LF. The HMG/LF pattern was identified as an indicator of the most severe AS with preserved cardiac reserve that allows to produce a gradient of more than 40 mmHg despite the LF. This condition, similarly to the “high mean gradient/high flow” pattern, is a strong independent determinant of a poor prognosis compared with the “low mean gradient/normal flow” pattern. However, it is related to an exceptionally good prognosis after surgery compared with medical treatment. Briand et al. have been the first to show that arterial stiffening characterized by reduced systemic arterial compliance increases global left ventricular load and may result in the LF.

The aim of the current study was to assess the potential effect of cardiac collagen metabolism on the HMG/LF phenomenon in patients with severe AS and to determine a clinical and echocardiographic pattern of these patients.

**PATIENTS AND METHODS** The study included a total of 89 patients with severe, degenerative AS and preserved LVEF, aged over 64 years. According to the European Society of Echocardiography/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines, AS was defined as severe when an HMG exceeded 40 mmHg and AVA indexed by the body surface area (BSA) of less than 0.6 cm²/m². Patients were classified as symptomatic if the cardinal manifestations of AS were observed, namely, angina, syncope on exertion, or heart failure of at least functional class II of the New York Heart Association classification. The left ventricular (LV) systolic function was classified as preserved when the LVEF was at least 50%. A coronary angiography was performed in all patients and significant coronary artery disease was diagnosed when the most severe reduction of the coronary artery diameter exceeded 50%. During the study, some patients were treated with angiotensin-converting enzyme inhibitors (ACEIs, n = 12), diuretics (n = 39), β-blockers (n = 14), and statins (n = 46). The exclusion criteria were as follows: another significant valvular heart disease (moderate-to-severe aortic insufficiency or mitral valve disease), a history of myocardial infarction, permanent stimulation, atrial fibrillation, uncontrolled hypertension, current inflammatory diseases, severe pulmonary, liver, or kidney disease, abnormal thyroid function, and inadequate echocardiographic imaging. Patients were divided into 2 groups: with an HMG and normal stroke (NF) defined as an SVI of at least 35 ml/m² (n = 70), and with an HMG and low stroke (low flow) defined as an SVI of less than 35 ml/m² (n = 19).

**Echocardiographic, conventional Doppler, and tissue Doppler examination** All patients underwent a comprehensive echocardiographic examination including M-mode, B-mode, conventional, and tissue Doppler echocardiography with the S3 probe (HP/Philips Sonos 5500). Blood pressure was measured immediately before echocardiographic and Doppler studies and was postponed in patients with blood pressure exceeding 140/90 mmHg until it normalized. All echocardiography recordings were stored and reanalyzed offline by 2 independent cardiologists experienced in echocardiography.

1 The severity of valvular obstruction was assessed based on the AVA calculated with the continuity equation indexed by the BSA (AVAI), peak velocity, and HMG across the aortic valve calculated with the Bernoulli’s equation. Stroke volume (SV) was measured at the LV outflow tract and indexed by the BSA (SVI). Additionally, an energy loss index (ELI) was assessed. The ELI was calculated using the following formula: ELI = [(AVA × AVA)/(AVA – AVAI)]/BSA, where AVA denotes aortic cross-sectional area derived from the diameter of the aorta measured at the sinotubular junction.2

2 The LV systolic function was assessed using the following parameters: LVEF calculated with the biplane Simpson’s method; midwall fractional shortening (MFS) calculated from the measurements of the posterior wall thickness (PWT) and LV internal dimension (LVID) at end-diastolic (LVIDd) and end-systolic (LVIDs) phases with the following formula: MFS = (LVIDd/2 + PWTd/2) – (LVIDs/2 + PWTs/2)/(LVIDd/2 + PWTd/2); stroke work (SW) using the following formula: SW = (mean arterial pressure [MAP] + HMG) × SV × 0.0136; and longitudinal systolic function by means of mitral annular average systolic velocity (S’) assessed for the septal and lateral sites.

3 To assess LV diastolic function the following parameters were measured: early (E) and late (A) transmitial peak flow velocities as well as mitral annular average E (E’) velocities assessed for septal and lateral sites. The E/A and E/E’ ratios were subsequently calculated. The left atrial volume was determined with the biplane Simpson’s method and indexed by the BSA (left atrial volume index [LAVI]).

4 The LV mass (LVM) and geometry. Interventricular septum diastolic thickness (IVSd), PWTd, and LVIDd were measured to calculate the LVM using the formula of the American Society of Echocardiography modified by Devereux: LVM = 0.8 × 1.04 × [(LVIdd + IVSd + LVIDd)/3 × sqrt(BSA)].
Table 1: Clinical characteristics and blood test results in the study groups

|                     | Low flow SVI <35 ml/m² (n = 19) | Normal flow SVI ≥35 ml/m² (n = 70) | P value |
|---------------------|---------------------------------|-----------------------------------|---------|
| age, y              | 74.47 ±4.66                     | 70.76 ±4.36                      | <0.01   |
| male, n (%)         | 7 (37)                          | 34 (49)                          | NS      |
| body mass index, kg/m² | 27.94 ±3.61               | 27.50 ±5.06                      | NS      |
| symptoms, n (%)     | 16 (84)                         | 49 (70)                          | NS      |
| significant coronary artery disease, n (%) | 10 (53)                              | 40 (58)                          | NS      |
| hypertension, n (%) | 14 (74)                         | 47 (67)                          | NS      |
| diabetes, n (%)     | 5 (26)                          | 17 (24)                          | NS      |
| hypercholesterolemia, n (%) | 11 (58)                              | 32 (48)                          | NS      |
| smoking, n (%)      | 4 (21)                          | 16 (23)                          | NS      |
| heart rate, bpm     | 69.42 ±6.14                     | 67.34 ±7.40                      | NS      |
| systolic blood pressure, mmHg | 128.16 ±10.70                     | 132.50 ±11.25                    | NS      |
| diastolic blood pressure, mmHg | 71.32 ±6.31                      | 74.79 ±6.89                      | NS      |
| pulse pressure, mmHg | 56.84 ±9.75                      | 57.71 ±7.69                      | NS      |
| mean arterial pressure, mmHg | 90.26 ±7.94                      | 94.02 ±7.79                      | NS      |
| NT-proBNP, pg/ml    | 1264.97 ±702.24                 | 716.70 ±488.78                   | <0.001  |
| CTX, ng/ml          | 6.48 ±1.60                      | 5.81 ±1.67                       | NS      |
| PIIINP, ng/ml       | 5.77 ±1.29                      | 4.89 ±1.36                       | <0.05   |
| MMP-9, ng/ml        | 5.92 ±2.47                      | 5.80 ±3.18                       | NS      |
| TIMP-1, ng/ml       | 297.37 ±86.27                   | 260.86 ±71.56                    | NS      |
| MMP-9/TIMP-1        | 2.27 ±0.97                      | 2.22 ±1.09                       | NS      |

Data are presented as mean ± standard deviation or number (percentage) of patients.

Abbreviations: CTX – carboxyterminal telopeptide of collagen type I, MMP-9 – matrix metalloproteinase 9, NS – nonsignificant, NT-proBNP – N-terminal pro-B-type natriuretic peptide, PIIINP – procollagen III N-terminal propeptide, SVI – stroke volume index, TIMP-1 – tissue inhibitor of matrix metalloproteinase type 1.

Biochemical measurements: Fasting venous blood samples were collected and plasma was frozen at −70°C until assayed for N-terminal pro-B-type natriuretic peptide (NT-proBNP), markers of collagen turnover. Plasma NT-proBNP concentrations were assessed by an electroeluminescence immunoassay with the Elecsys® NT-proBNP kit on the Elecsys® 1010 analytical system (Roche Diagnostics). The serum concentration of procollagen III N-terminal propeptide (PIIINP), a marker of collagen synthesis, was assessed using a quantitative radioimmunoassay (Orion Diagnostica UniQ, Espoo, Finland). The circulating levels of matrix metalloproteinase 9 (MMP-9) and carboxyterminal telopeptide of collagen type I (CTX), as markers of extracellular collagen degradation, and the tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1; the most relevant physiological inhibitor of MMP-9) were determined by quantitative sandwich enzyme immunoassays (Quantikine Human MMP-9 Immunoassay and Quantikine Human TIMP-1 Immunoassay, R&D Systems Inc, Minneapolis, Minnesota, United States; Orion Diagnostica UniQ for CTX).

The study was approved by the Ethics Committee of the Medical University of Łódź, and each patient provided a written informed consent.

Statistical analysis: Continuous data were expressed as mean ± standard deviation. Variables were log-transformed before the statistical analysis, if necessary. Differences between the groups were compared using the t test or Mann–Whitney test, as appropriate. Categorical variables were presented as a number and percentage of patients, and comparisons between the analyzed groups were performed with the χ² test. Associations between the LF (SVI <35 ml/m²) and the analyzed biochemical and echocardiographic parameters were examined using the Pearson’s or Spearman’s correlation coefficient, as appropriate. A P value of less than 0.05 was considered statistically significant.
Comparison of the echocardiographic parameters of cardiac structure and function in the study groups

| Low flow SVI <35 ml/m² (n = 19) | Normal flow SVI ≥35 ml/m² (n = 70) | P value |
|---------------------------------|-----------------------------------|--------|
| LVIDd, cm                       | 4.71 ±0.41                        | 5.02 ±0.42 | <0.01 |
| LViSd, cm                       | 3.01 ±0.35                        | 3.10 ±0.41 | NS    |
| IVSTd, cm                       | 1.38 ±0.13                        | 1.33 ±0.11 | NS    |
| PWtd, cm                        | 1.20 ±0.08                        | 1.17 ±0.12 | NS    |
| LVM, g                          | 237.79 ±42.45                     | 250.64 ±47.77 | NS    |
| LVMI, g/m²                      | 132.67 ±28.14                     | 138.57 ±27.00 | NS    |
| RWT                             | 51.46 ±5.83                       | 46.84 ±5.77 | <0.01 |
| LVEDV, cm²                      | 85.00 ±15.04                      | 93.51 ±15.93 | <0.05 |
| LVESV, cm²                      | 34.21 ±6.40                       | 34.90 ±10.04 | NS    |
| LV ejection fraction,%          | 60.84 ±4.91                       | 62.26 ±5.12 | NS    |
| MFS, %                          | 20.76 ±3.79                       | 23.24 ±3.36 | <0.01 |
| SW, g × m                       | 104.71 ±23.67                     | 164.11 ±27.62 | <0.0001 |
| SV, m²                          | 29.21 ±3.50                       | 45.52 ±5.08 | <0.0001 |
| SVI, m³/m²                      | 53.03 ±8.64                       | 82.63 ±12.2 | <0.0001 |
| CO, ml/min                      | 3.71 ±0.83                        | 5.56 ±0.97 | <0.0001 |
| E/A                             | 0.99 ±0.36                        | 0.87 ±0.31 | NS    |
| mitral annular mean E (E') velocity, cm/s | 5.05 ±1.10                     | 5.71 ±1.26 | <0.05 |
| mitral annular mean S (S') velocity, cm/s | 5.68 ±1.12                     | 6.58 ±1.42 | <0.05 |
| E/E'                            | 15.80 ±4.13                       | 12.50 ±3.27 | <0.001 |
| LA, cm                          | 4.11 ±0.30                        | 3.77 ±0.56 | <0.01 |
| LAV, cm²                        | 76.05 ±9.26                       | 68.51 ±8.55 | <0.01 |
| LAVI, c m³/m³                   | 42.11 ±5.09                       | 37.97 ±5.27 | <0.01 |

Abbreviations: CO – cardiac output, IVSTd – interventricular septum diastolic thickness, LA – left atrium, LAV – left atrial volume, LAVI – left atrial volume index, LVEDV – left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, LVIDd – left ventricular internal diastolic dimension, LViSd – left ventricular internal systolic dimension, LVMI – left ventricular mass index, MFS – midwall fractional shortening, PWtd – posterior wall diastolic thickness, RWT – relative wall thickness, SV – stroke volume, SW – stroke work, others – see TABLE 1.

RESULTS
In the group of 89 patients with severe, degenerative AS, preserved LVEF, and HMG, there were 70 patients (79%) with the HMG/NF pattern (SVI, 45.51 ±5.07 ml/m²) and 19 patients (21%) with the HMG/LF pattern (SVI, 29.21 ±3.51 ml/m²).

As shown in TABLE 1, patients in the HMG/LF group were significantly older and had higher NT-proBNP and PIIINP levels compared with the HMG/NF group. There were no significant differences in terms of ACEI, diuretic, β-blocker, and statin use between the study groups.

TABLE 2, which compares the echocardiographic parameters of cardiac structure and function between the study groups, shows that LV end-diastolic dimension and volume were significantly smaller and RWT higher in the HMG/LF group, indicating a more pronounced concentric remodeling in these patients. Moreover, these patients had larger left atrial dimension and volume, while they had lower values of MSF, SW, and S' despite similar LVEF. Finally, they had lower mitral flow E velocities and higher values of the E/E'.

The echocardiographic parameters of the severity of AS and systemic arterial hemodynamics are presented in TABLE 3. The HMG/LF group had lower AVA, AVAI, ELL, CO, and SAC, higher SVR and Zsw, and a similar HMG compared with the other group.

We revealed significant correlations in the whole study group between the SVI and the blood levels of NT-proBNP (r = –0.34, P < 0.001) and PIIINP (r = –0.21, P < 0.05) as well as several echocardiographic parameters of cardiac structure and function, namely, LAVI (r = –0.29, P < 0.01), RWT (r = –0.35, P < 0.001), MSF (r = –0.34, P < 0.01), E (r = –0.23, P < 0.05), E' (r = 0.29, P < 0.01), S' (r = 0.31, P < 0.01), and E/E' (r = –0.39, P < 0.001).

DISCUSSION
The principal findings of our study are a significantly higher PIIINP level in the HMG/LF group compared with the HMG/NF group of patients with severe degenerative AS and an inverse correlation between PIIINP levels and the SVI. This suggests that there is a link between collagen metabolism in the extracellular
matrix and the pathogenesis of the LF pattern. In the previous studies, the PIIINP level was related to the deterioration of the LV function in AS and to several anatomic and functional alterations in hypertensive heart disease, providing indirect diagnostic data on myocardial fibrosis. Although hypertension has a more significant effect on the whole circulatory system than AS, the burden for the LV seems to be comparable in these conditions. Animal and clinical studies in hypertension have demonstrated that myocardial fibrosis rather than myocyte hypertrophy is a predominant factor responsible for diastolic dysfunction. 17-19 LV myocardial samples from patients with AS have shown that the balance between MMPs and TIMPs is shifted towards MMP inhibition that may facilitate collagen accumulation. 4 Indeed, in our HMG/LF group, when compared with the HMG/NF group, LVM did not differ significantly, diastolic dysfunction was more advanced, and noticeably higher plasma levels of TIMP-1 and lower MMP-9-to-TIMP-1 ratio were detected, although the differences were not significant. Different observations and conclusions come from the study by Polyakova et al. 7 on myocardial tissue samples of patients with AS. The authors noted that the upregulation of MMPs and inadequate inhibition by TIMPs with a paradoxical MMP-mediated “abnormal” collagen accumulation was possibly due to the activity of MMP side products. Thus, considering the combination of specific biological and physical stimuli, the exact action of MMPs and TIMPs as the major proteolytic system for the extracellular matrix in pressure-overloaded, hypertrophied human myocardium still needs elucidation.

Our results showed that, in patients with HMG, the LF implies a more advanced disease, and this applies to older patients with higher LV afterload. In agreement with the previous studies, 11,12,20,21 we showed that the HMG/LF group has a more severe, double burden imposed on the LV at the level of the aortic valve as expressed by lower AVAI and ELI and systemic arterial bed as indicated by lower SAC and higher SVR and Z

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Excessive pressure load imposed on the LV is associated with LV concentric remodeling. 22 It explains higher RWT in the HMG/LF group, as revealed in our study and by a number of other investigators. 20,21 Diastolic function appears early in the course of AS, 23,24 and, in our study, it was more advanced in the HMG/LF group compared with the HMG/NF group. It was expressed as bigger left atria, lower mitral flow E velocities, and higher values of the E/E’. Of note, preserved LVEF does not explicitly represent preserved systolic function. A depressed longitudinal LV systolic function is dependent on the subendoocardial fibers, which are first exposed to maldistribution of blood in a hypertrophied myocardium due to the augmented wall stress, and was observed even in asymptomatic patients with severe AS. 8,25 This explains why S’ myocardial velocity, which depicts longitudinal systolic LV properties, was significantly lower in HMG/LF patients in a number of studies, including ours. In this group, we also revealed lower (although not significantly) MSF, which reflects a decrease in the radial function. This observation is supported by previous studies. 20,21,26 Lancellotti et al., 26 using speckle-tracking echocardiography, revealed that impaired circumferential myocardial deformation together with left atrial area index are good indicators of the LF or increased afterload in AS. Even subclinical LV systolic dysfunction and its emptying properties together with impaired filling may both contribute to a decrease in SV.

Higher NT-proBNP levels observed in our HMG/LF group can be explained by a previously documented complex relation between brain natriuretic peptides and the severity of AS. 37,38 myocardial stiffness, 29 LV diastolic dysfunction, 20,21 and aortic stiffening. 32,33

We have shown that the group of patients with severe AS and preserved LVEF is not homogenous but rather that each patient may have a different outcome. Most patients with the HMG/LF pattern are symptomatic and, according to the ESC/EACTS guidelines, they are referred for surgery. However, even in patients without this classic presentation, the LF pattern should reinforce the decision to refer a patient for surgery because it is associated with excellent postoperative survival. 11 In HMG/LF patients
with reduced LVEF, which seems to be the next step in cardiac decompensation, preoperative systolic and diastolic LV dysfunction is the major predictor of mortality following aortic valve replacement.34

The present study supports the need for a more comprehensive assessment of patients with AS. First of all, it confirms the importance of AVA and LV geometry evaluation as well as of a thorough insight into the systolic and diastolic LV function. The finding of a relatively small LV with a higher RWT, borderline or low LVEF, low SW, MFS, and depressed longitudinal systolic function on tissue Doppler imaging should assure the physician that the diagnosis of severe AS guided by the calculation of the AVA is reliable and that transvalvular gradient is possibly underestimated. Further quantification of vascular and global LV load may confirm the diagnosis and reveal the underlying pathology. The pseudonormal filling pattern is common in severe AS; therefore, the measures to identify this anomaly, most easily with tissue Doppler imaging should be undertaken in all patients. High blood NT-proBNP levels may confirm the severity of AS with subsequent alterations to the myocardial structure and hemodynamics.

Conclusions In patients with severe AS, HMG and preserved LVEF, LP is related to more severe valvular obstruction, altered aortic hemodynamics, and a higher degree of cardiac deterioration as shown by Doppler echocardiography and high NT-proBNP levels. A significant inverse correlation between the SVI and PIIINP levels may indicate enhanced tissue fibrosis as an underlying pathology.

Study limitations The major limitation of the current study is a small sample size and lack of follow-up. We are planning to continue our research to show how the LF pattern affects the outcome after aortic valve replacement. A good postoperative prognosis in these patients indicates that the elimination of the burden of the stenotic valve has a stronger effect on the outcome than persistent elevated aortic stiffness.

A possible pitfall in the assessment of the AVA is an improper measurement of the left ventricular outflow tract (LVOT) diameter and velocity time integral at the level of the LVOT and aortic valve. However, we have made every effort to perform careful and detailed echocardiographic examinations according to the European Association of Echocardiography/American Society of Echocardiography recommendations for the echocardiographic assessment of valve stenosis.35 More over, we assessed the ELI, which has been shown to be more closely related to an increase in LV workload than the AVA.31 In view of the observations made by Michlina et al.,34 in our HMG/LF patients who had small LVOTd (defined as 1.7–1.9 cm), the underestimation of the AVA calculated with the Bernoulli’s equation might be suggested. Still, we showed that not only the AVAI but also the ELI were lower in the HMG/LF group.

We assessed arterial stiffness using only the indirect measures of SAC and SVR, but the direct measure of carotid–femoral pulse wave velocity, which is the gold standard in daily practice, was not performed.

The expression of collagen metabolism biomarkers in response to various biological and physical stimuli is cell-specific and may differ among multiple myocardial cell types and should be interpreted with caution. Other sources of collagen turnover markers might have affected their plasma levels, but the exclusion criteria in the present study, including coexisting conditions leading to fibrosis, potentially diminish the significance of this factor. In view of the arterial–ventricular coupling, an increased arterial and cardiac wall stiffness with aging might affect the comparative results of our different age groups.34

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Obraz kliniczny i echokardiograficzny oraz biomarkery neurohormonalne i przemiany kolagenu u chorych z ciężką, niskoprzepływową stenozą aortalną, z wysokim gradientem przezastawkowym

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SŁOWA KLUCZOWE
N-końcowy propeptyd natriuretyczny, stenosa aortalna, wskaźniki przemiany kolagenu

STRESZCZENIE
WPROWADZENIE U chorych z ciężką stenozą aortalną (SA), wysokim średnim gradientem przezastawkowym (high mean gradient – HMG) i zachowaną frakcją wyrzutową lewej komory (left ventricular ejection fraction – EF) można zaobserwować paradoksalnie niski przepływ (low flow – LF).

CELE Celem badania była ocena potencjalnego związku między metabolizmem kolagenu w mięśniu sercowym, a zjawiskiem „HMG/LF” oraz określenie klinicznego i echokardiograficznego wzorca tej grupy pacjentów.

PACJENCI I METODY Oceniano stan kliniczny u 89 chorych z ciężką SA, HG i zachowaną EF (≥50%), w wieku >64. rż. Parametry struktury i funkcji serca oraz wskaźniki hemodynamiczne systemowego łożyska tętniczym oznaczano metodą echokardiografii, doplerowskiego badania echokardiograficznego oraz doplera tkankowego. Ponadto mierzono osoczowe poziomy: N-końcowego propeptydu natriuretycznego typu B (NT-proBNP), N-końcowego propeptydu kolagenu typu III (PIIINP), C-końcowego telopeptydu kolagenu typu I (CITP), metaloproteinazy macierzy zewnętrzkomórkowej-9 i inhibitora metaloproteinazy macierzy zewnętrzkomórkowej typu 1. Analizie poddano dwie grupy pacjentów: z „normalnym przepływem” [stroke volume index – SVI] ≥35ml/m²; n = 70) i z LF (SVI <35 ml/m²; n = 19).

WYNIKI Pacjenci z LF byli starsi, mieli większy wymiar lewego przedsionka i wskaźnik objętości lewego przedsionka, mniejszą powierzchnię zastawki aortalnej, wskaźnik utraty energii, pracę wyrzutu, falę E napływu mitralnego, prędkość E’ i S’ ruchu pierścienia mitralnego i podatność tętnic systemowej oraz większą względną grubość ścian lewej komory, E/E’, opór tętnic systemowych i impedancję zastawkowo –tętniczą. Wykazano korelację między SVI a NT-proBNP i PIIINP oraz wybranymi wskaźnikami struktury i funkcji serca.

WNIOSKI U chorych z ciężką AS, HMG i zachowaną LVEF LF jest związany z bardziej zaawansowaną wadą, zmianą hemodynamicznych właściwości aorty, dysfunkcją serca oraz większym stężeniem NT-proBNP we krwi. Ujemeza zależność między PIIINP i SVI może wskazywać na nasilony proces zwłóknienia tkankowego jako przyczynę sprawczą.