

The change in NT-pro-BNP and post-PTMC echocardiography parameters in patients with mitral stenosis. A pilot study

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Background. The change in the level of NT-pro-BNP (N-terminal-pro-Brain Natriuretic Peptide) is now considered as a reflection of the hemodynamic alterations and its circulatory reductions reported early after successful PTMC (percutaneous transvenous mitral commissurotomy). The present study aims to assess the change in the level of NT-pro BNP following PTMC in patients with mitral stenosis and also to determine the association between circulatory NT-pro-BNP reduction and post-PTMC echocardiography parameters.

Methods. Twenty five symptomatic consecutive patients with severe MS undergoing elective PTMC were prospectively enrolled. All patients underwent echocardiography before and also 24 to 48 hours after PTMC. Peripheral blood samples were taken for measurement of NT-pro-BNP before as well as 24 to 48 hours after PTMC. The patients were also classified in group with normal sinus rhythm or having atrial fibrillation (AF) based on their 12-lead electrocardiogram.

Results. It was shown a significant decrease in the parameters of PPG (Peak Pressure Gradient), MPG (Mean Pressure Gradient), PHT (Pressure Half Time), PAP (Pulmonary Arterial Pressure), LAV (Left Atrial Volume), and also a significant increase in MVA (Mitral Valve Area) RVS (Right Ventricular S velocity), and strains of lateral, septal, inferior and anterior walls of LA following PTMC. The mean LVEF remained unchanged after PTMC. The mean NT-pro-BNP before PTMC was 309.20 ± 17.97 pg/lit that significantly diminished after PTMC to 235.72 ± 22.46 pg/lit ($p = 0.009$). Among all echocardiography parameters, only MPG was positively associated with the change in NT-pro-BNP after PTMC. Comparing the change in echocardiography indices between the patients with normal rhythm and those with AF, lower change in PAP was shown in the group with AF. However, more change in the level of NT-pro-BNP after PTMC was shown in the patients with AF compared to those without this arrhythmia.

Conclusion. PTMC procedure leads to reduce the level of NT-pro-BNP. The change in NT-pro-BNP is an indicator for change in MS severity indicated by decreasing MPG parameter. Lower change in PAP as well as higher change in NT-pro-BNP is predicted following PTMC in the group with AF compared to those with normal sinus rhythm.

Keywords: pro-brain natriuretic peptide, Mitral Valve Stenosis, Echocardiography.

INTRODUCTION

N-terminal pro b-type natriuretic peptide (NT-pro-BNP) is essentially applied to evaluate and diagnose the severity of heart failure [1]. In fact, cardiac ventricular myocytes constitute the main source of this activated peptide and thus its rise is evident when the heart is abnormally stretched in cases with heart failure, valvular heart diseases and even cardiac ischemic events [2, 3]. Moreover, the increase in this biomarker can predict the risk for recurrent cardiac events and poor outcome of

cardiac surgical procedures [4]. Recent studies have identified this marker as a precious indicator of the severity of valvular heart disease, in addition to other basic assessments including clinical and echocardiographic evaluations [5, 6]. On the other hand, the level of NT-pro BNP levels has been revealed to correlate directly with the severity of mitral stenosis and thus considerable reduction of this marker is predictable after successful correction of the stenotic valve [7]. Physiologically, since percutaneous transvenous mitral commissurotomy (PTMC) as a choice treatment approach in patients

with mitral stenosis leads to rapid decreases in left atrial pressures and subsequent decreases in pulmonary artery pressure (PAP), it is possible that the change in the level of NT-pro-BNP may be considered as a reflection of the hemodynamic alterations [8]. Thus, reduction in circulatory level of NT-pro-BNP levels can be reported early after successful PTMC [9, 10]. The present study intends to assess the change in the level of NT-pro-BNP following PTMC in patients with mitral stenosis and the association between circulatory NT-pro-BNP reduction and post-PTMC echocardiography parameters. Also, the association between lowering PAP after PTMC and the level of NT-pro BNP was assessed.

MATERIALS AND METHODS

In total, 25 symptomatic consecutive patients with severe MS (based on the measurement of mitral valve area) undergoing elective PTMC in Modarres Hospital in 2014-2015 were enrolled prospectively. The cutoff value used to recommend the procedure was mitral valve area in planimetry $< 1.5 \text{ cm}^2$. A written informed consent was obtained from all subjects before participation in the study. Exclusion criteria were left ventricular ejection fraction (LVEF) less than 50%, history of systemic hypertension, history of myocardial infarction or known coronary artery disease, renal failure of stage 3 or higher, severe chronic obstructive pulmonary disease, incomplete echocardiography data, thrombus in left atrium or left appendage and pulmonary edema. Demographic and anthropomorphic data including age, gender, height and weight, and body mass index (BMI) were collected and recorded. The patients were also classified in group with normal sinus rhythm or having atrial fibrillation (AF) based on their 12-lead electrocardiogram. Clinical information such as heart rhythm, and history of comorbid diseases were also gathered. All patients underwent echocardiography before and also 24 to 48 hours after PTMC to measure echocardiography parameters including mitral valve area (MVA), peak pressure gradient (PPG), mean pressure gradient (MPG), pressure half-time (PHT), right ventricular end diastolic diameter (RVEDD), right ventricular annular S velocity (RVS), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery pressure (PAP), left atrial volume in the apical 4-chamber view (4C) and apical 2-chamber view (LAV2c and LAV4c), and also strains of lateral, septal, inferior and anterior walls of LA by tissue Doppler imaging. Peripheral blood samples for measurement of

NT-pro BNP were taken from all patients before as well as 24 to 48 hours after PTMC procedure. NT-pro-BNP of greater than 125 pg/mL was defined indicator of cardiac dysfunction. PTMC was executed *via* a femoral approach with the patient under conscious sedation. Successful PTMC was defined as $\text{MVA} \geq 1.5 \text{ cm}^2$ or $\geq 1 \text{ cm}^2/\text{m}^2$ without significant complications including new mitral regurgitation or acceleration of previous mild mitral regurgitation.

For statistical analysis, quantitative variables were presented as mean \pm standard deviation and categorical variables were presented by absolute frequencies and percentages. The change in study parameters after PTMC was assessed using the paired t test or Wilcoxon test. The correlation between quantitative parameters was tested using the Pearson's or Spearman's correlation coefficient tests. P values of ≤ 0.05 were considered statistically significant. Data were analyzed using IBM SPSS statistical software version 21.0 (Armonk, NY: IBM Corp.).

RESULTS

The mean age of participants was 44.36 ± 11.36 years ranged 24 to 65 years and 84% were male. Regarding cardiac rhythm status, 60% had normal sinus rhythm, while 40% had AF. The considered etiology of mitral stenosis was rheumatic involvement due to history and echocardiographic findings. 18 patients were new cases of mitral stenosis who did not receive any medical treatment before diagnosis of mitral stenosis; 7 patients were known cases of mitral stenosis who were under treatment of warfarin and low dose diuretic. 17 patients had score of 8 and 8 patients had score of 7, according to Wilkins score in echocardiography. Table 1 summarizes echocardiography parameters before and after PTMC in affected patients. According to these results, it was shown a considerable decrease in the parameters of PPG, MPG, PHT, PAP, LAV, and a significant increase in other parameters including MVA, RVS velocity, and LA strain of lateral, septal, inferior and anterior walls following PTMC. The mean LVEF remained unchanged after PTMC. The mean NT-pro-BNP before PTMC was $309.20 \pm 17.97 \text{ pg/lit}$ that notably reduced after PTMC to 235.72 ± 22.46 ($p = 0.009$). As shown in Table 2 and Figure 1, among all echocardiography parameters, only MPG was positively associated with the change in NT-pro-BNP after PTMC. Comparing the change in echocardiography indices between the patients with normal rhythm and those with AF (Table 3) lower

change in PAP was shown in the group with AF in comparison with the group with normal sinus rhythm (8.00 ± 6.94 versus 22.47 ± 13.31 , $p < 0.001$). However, more change in the level of NT-pro-BNP after PTMC was shown in the patients

with AF compared to those without this arrhythmia (3.80 ± 0.15 versus 1.25 ± 0.07 , $p < 0.001$). There was no new significant mitral regurgitation or acceleration of mild mitral regurgitation after percutaneous transvenous mitral commissurotomy.

Table 1
Echocardiography parameters before and after PTMC

MVA(cm²)	0.97 ± 0.24	1.76 ± 0.21	< 0.001
PPG(mmHg)	23.21 ± 8.39	12.98 ± 4.11	< 0.001
MPG(mmHg)	11.94 ± 5.41	5.92 ± 3.00	< 0.001
PHT(msec)	211.48 ± 47.94	127.20 ± 29.61	< 0.001
RVEDD(mm)	30.76 ± 2.99	30.64 ± 2.99	0.327
RVS velocity(cm/sec)	11.56 ± 2.04	12.16 ± 1.95	0.001
TAPSE(mm)	21.20 ± 3.73	21.28 ± 3.66	0.425
PAP(mmHg)	55.52 ± 15.48	38.84 ± 8.64	< 0.001
LAV (2ch)(cc)	68.28 ± 12.48	66.72 ± 12.81	< 0.001
LAV (4ch)(cc)	89.16 ± 23.16	83.32 ± 17.56	0.004
Strain (lateral)%	20.96 ± 30.53	22.52 ± 6.95	< 0.001
Strain (septal)%	22.36 ± 7.47	23.40 ± 7.63	< 0.001
Strain (inferior)%	21.92 ± 2.66	23.36 ± 10.05	< 0.001
Strain (anterior)%	21.72 ± 9.24	22.72 ± 8.84	0.030

Abbreviations: MVA: Mitral valve area; PPG: Peak pressure gradient; MPG: Mean pressure gradient; PHT: Pressure half-time; RVEDD: Right ventricular end diastolic diameter; RVS: Right ventricular S; TAPSE: Tricuspid annular plane systolic excursion; PAP: Pulmonary arterial pressure; LAV: Left atrial volume.

Table 2
Association between the change in NT-pro-BNP and the change in echocardiography parameters after PTMC

MVA	-0.308	0.134
PPG	0.128	0.541
MPG	0.462	0.020
PHT	0.157	0.455
RVEDD	0.206	0.323
RVS velocity	-0.124	0.524
TAPSE	0.322	0.117
PAP	0.342	0.094
LAV (2ch)	0.248	0.233
LAV (4ch)	0.232	0.264
Strain (lateral)%	-0.257	0.215
Strain (septal)%	-0.039	0.854
Strain (inferior)%	-0.061	0.771
Strain (anterior)%	0.048	0.819

Abbreviations: MVA: Mitral valve area; PPG: Peak pressure gradient; MPG: Mean pressure gradient; PHT: Pressure half-time; RVEDD: Right ventricular end diastolic diameter; RVS: Right ventricular S; TAPSE: Tricuspid annular plane systolic excursion; PAP: Pulmonary arterial pressure; LAV: Left atrial volume.

Table 3

Change in study parameters following PTMC in the groups with and without AF

NT-Pro-BNP(pg/lit)	3.80 ± 0.15	1.25 ± 0.07	< 0.001
MVA(cm²)	0.77 ± 0.22	0.81 ± 0.21	0.681
PPG(mmHg)	9.06 ± 4.81	11.01 ± 6.73	0.438
MPG(mmHg)	4.36 ± 2.53	7.13 ± 4.28	0.079
PHT(msec)	66.80 ± 34.51	95.93 ± 47.04	0.107
RVEDD(mm)	0.15 ± 0.10	0.20 ± 0.77	0.426
RVS velocity(cm/sec)	0.60 ± 0.70	0.60 ± 0.83	0.999
TAPSE(mm)	0.20 ± 0.42	0.01 ± 0.53	0.331
PAP(mmHg)	8.00 ± 6.94	22.47 ± 13.31	0.005
LAV (2ch)	2.30 ± 2.79	2.73 ± 2.34	0.679
LAV (4ch)	3.10 ± 3.07	7.67 ± 11.34	0.229
Strain (lateral)%	1.00 ± 0.47	1.93 ± 2.19	0.200
Strain (septal)%	0.80 ± 0.63	1.20 ± 1.37	0.400
Strain (inferior)%	0.90 ± 0.99	1.80 ± 2.11	0.223
Strain (anterior)%	1.30 ± 1.06	0.80 ± 2.68	0.582

Abbreviations: MVA: Mitral valve area; PPG: Peak pressure gradient; MPG: Mean pressure gradient; PHT: Pressure half-time; RVEDD: Right ventricular end diastolic diameter; RVS: Right ventricular S; TAPSE: Tricuspid annular plane systolic excursion; PAP: Pulmonary arterial pressure; LAV: Left atrial volume.

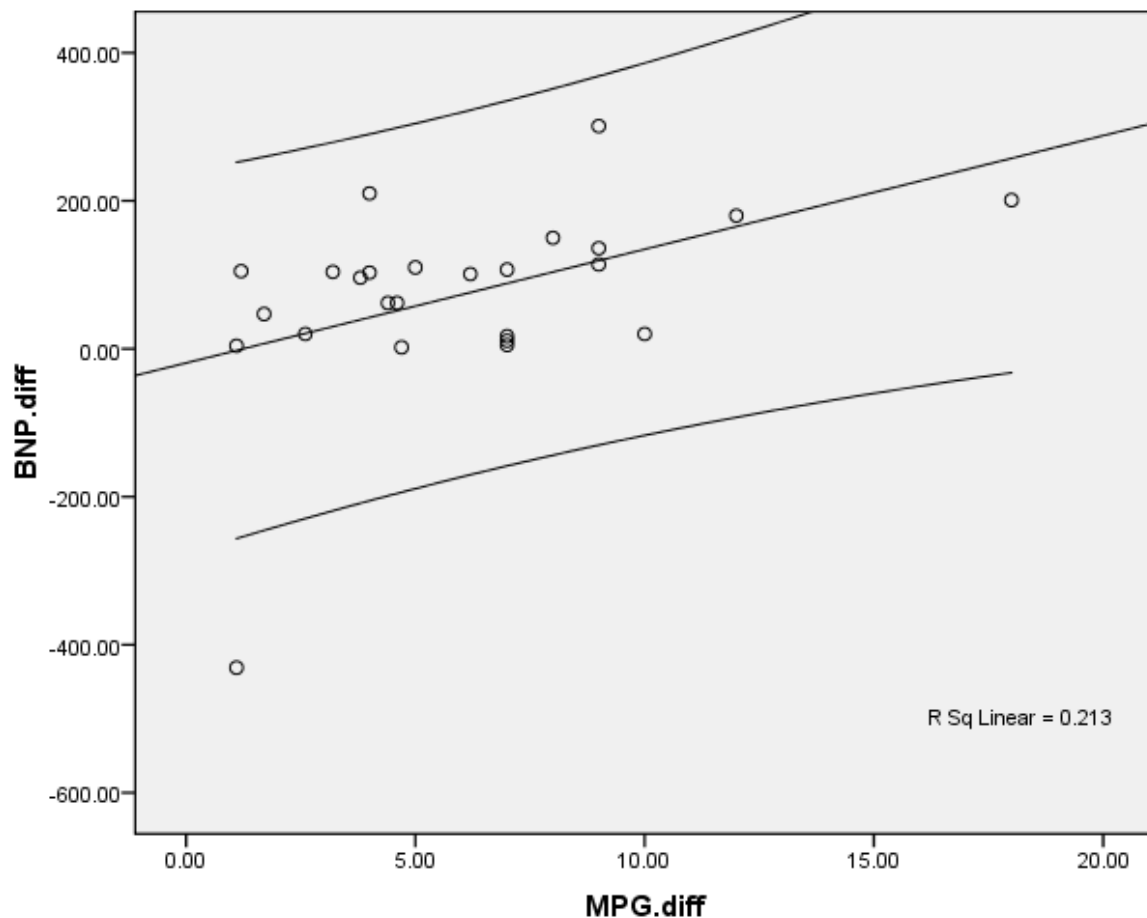


Figure 1. Association between BNP level and MPG.

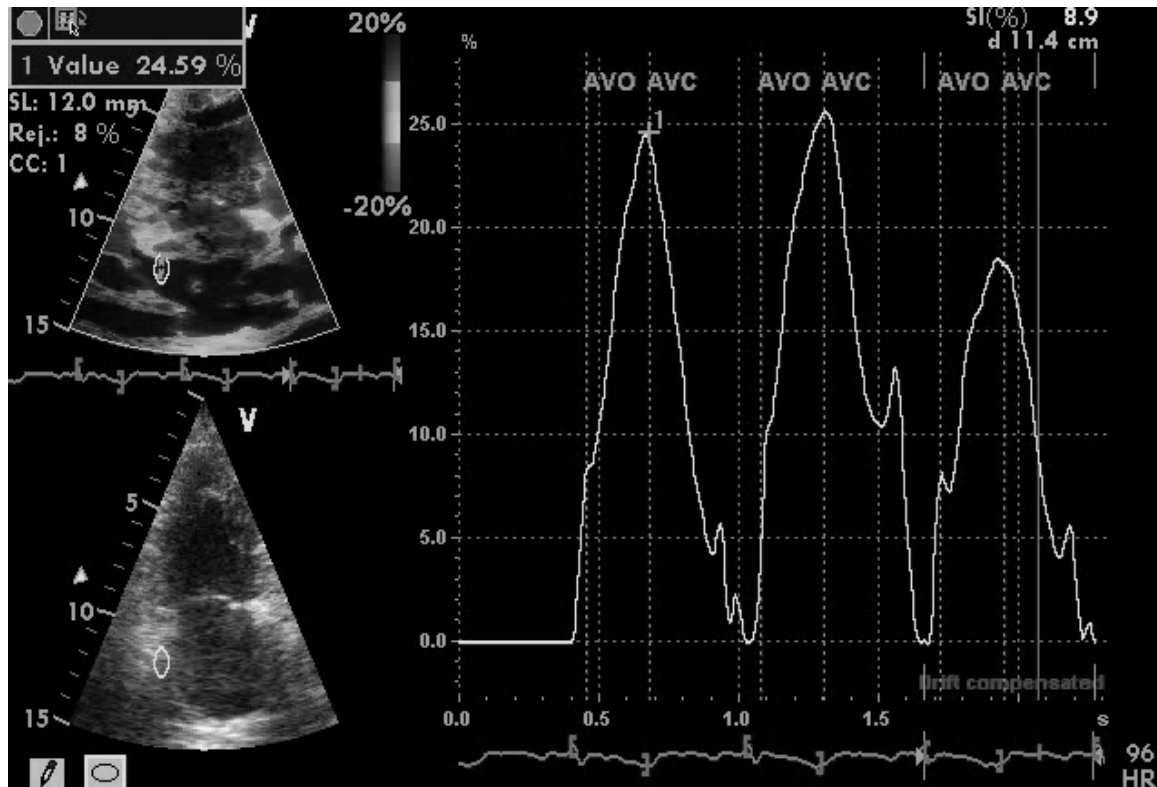


Figure 2. LA strain measurement based on tissue Doppler imaging.

DISCUSSION

According to previous findings on hormonal components secreted from atrial and ventricular cells in response to strain changes and wall motion abnormalities, the current study aimed to assess the relationship between the changes in NT-pro-BNP and echocardiography parameters. In this regard, the first imperative finding was that among all parameters, MPG was associated with the change in NT-pro-BNP. MPG is an indicator for valvular pressure gradient, particularly for mitral valve. In fact, the measurement of NT-pro-BNP can be used for assessing mitral stenosis severity as well. Similar to our study, Arat-Ozkan *et al.* [11] could show that patients with mitral stenosis had higher NT-pro-BNP levels compared to controls, but they also found a significant correlation between NT-pro-BNP and left atrial and right ventricular size as well as mitral valve area, mean mitral gradient, peak PAP and NYHA functional class. Interestingly, similar to our observation, they showed that those with atrial fibrillation had significantly higher NT-pro-BNP levels compared to those with sinus rhythm. In the same way, Eryol *et al.* [12] indicated that NT-pro-BNP level in the group with severe mitral stenosis was considerably higher than that in the mild mitral stenosis and, in fact, when patients were taken

together, as the area of the mitral valve decreased, the level of BNP underwent a corresponding increase. As shown by Iltumur *et al.* [13], NT-pro-BNP levels demonstrated a significantly greater increase in severe MS than in moderate MS; in their study, there was a positive correlation with pulmonary artery pressure and a negative correlation with mitral valve area. Some studies could also demonstrate high value of increasing level of NT-pro-BNP in differentiating severe mitral stenosis from mild type. So Uçar *et al.* [14] suggested that NT-pro-BNP value of 32 pg/mlit is the best cut-off value for the determination of patients with mitral stenosis with a positive predictive value of 100% and a negative predictive value of 75%.

Moreover, a cutoff value of total average LA strain (23.28%) can discriminate normal and abnormal LA function with a sensitivity of 93% and specificity of 100% and LA strain seems to be a better factor for diagnosis of abnormal LA function [15].

According to the present results, increase of the strain of LA walls to more than 23% is predictive for successful PTMC; however, the relation between NT-pro-BNP and LA strain and other echocardiography indices such as left atrial functional parameters and PAP remains questioned; thus it should be in detail assessed in further studies with a more number of patients.

As another essential finding, we showed that the presence of atrial fibrillation may confound the relation between NT-pro-BNP and echocardiography indices because of more change in the level of NT-pro-BNP after PTMC in the patients with AF compared to those with normal sinus rhythm. The association between NT-pro-BNP level and atrial fibrillation has been less studied and understood. Some studies have proved that NT-pro-BNP is increased in atrial fibrillation [16-19]. The proposed mechanisms are high frequency of atrial myocyte contraction and local atrial inflammation [18]. It has been also recommended that BNP increases within 4 hours from the onset of atrial inflammation; whether this applies to NT-pro-BNP is also not clear [20]. In demonstrating association between NT-pro-BNP and atrial fibrillation, it has been shown that NT-pro-BNP levels may drop after successful cardioversion of atrial inflammation [17]. Actually, the treatment of atrial inflammation can be reflected by reducing the level of NT-pro-BNP.

As the last point, lower change in PAP as well as higher change in NT-pro-BNP is predicted following PTMC in the group with AF compared to those with normal sinus rhythm in our study; this finding is relatively different from the findings of some other studies [21, 22]. Future studies with large sample size and powerful meta-analysis will reveal more detailed and clear results.

CONCLUSION

In conclusion, in parallel with previous studies, most atrial and ventricular function parameters in echocardiography improved significantly following PTMC and thus it seems that PTMC is an effective approach to improve cardiac functional indices. In this regard, it seems that improvement of some echocardiography indices such as MPG following PTMC can be predicted by measuring the level of NT-pro-BNP that can be used as an index of successful PTMC in a patient that we could not evaluate PTMC results such a poor echo window.

Introducere. Modificările nivelului NT-pro-BNP sunt considerate secundare modificărilor hemodinamice iar scăderea nivelului acestuia este reflectat după intervenție PTMC (comisurotomie percutană transvenoasă). Studiul își propune să evalueze modificările NT-pro-BNP după PTMC la pacienții cu stenoză mitrală și să evalueze asocierea dintre nivelurile circulatorii ale NT-pro-BNP și modificarea parametrilor ecocardiografici.

Materiale și metode. Au fost recrutați 25 de pacienți cu stenoză mitrală severă ce au suferit ulterior PTMC. Toți pacienții au fost evaluați ecocardiografic înainte și la 24 și 48 ore după PTMC. Au fost prelevate probe serologice pentru analiza NT-pro-BNP, înainte și la 24 și 48 ore post PTMC. Pacienții au fost clasificați în 2 grupe după analiza EKG: fie ritm sinusal sau fibrilație atrială.

Rezultate. După PTMC s-a observat o scădere semnificativă pentru PPG (Peak Pressure Gradient), MPG (Mean Pressure Gradient), PHT (Pressure Half Time), PAP (tensiunea pulmonară arterială), LAV (volumul atriului stâng) și o scădere a ariei valvei mitrale. Media fracției de ejeție a VS nu s-a modificat după PTMC. Valorile NT-pro-BNP înainte de PTMC au fost de $309,20 \pm 17,97$ pg/L și au scăzut semnificativ la $235,72 \pm 22,46$ pg/L după PTMC ($p = 0,009$).

Dintre toți parametrii ecocardiografici numai MPG s-a asociat pozitiv cu modificările NT-pro-BNP-ului. Comparând modificările parametrilor ecocardiografici între cei cu ritm sinusal și cei cu fibrilație atrială (AF), la cei cu AF au fost găsite modificări mai mici ale PAP. Valorile NT-pro-BNP-ului au suferit modificări mai mari în subgrupul de pacienți cu AF.

Concluzii. PTMC duce la scăderea NT-pro-BNP-ului. Modificările NT-pro-BNP-ului sunt un indicator pentru severitatea stenozei mitrale indicate prin scăderea parametrului MPG.

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