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The Correlation of NT-Pro BNP with Echocardiographic Indices Including 3D Vena Contracta Width in the Assessment of Severity of Mitral Regurgitation

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Abstract

Introduction: Mitral regurgitation (MR) is a common valvular disease that causes significant morbidity and mortality. The use of multiple echocardiographic indices and hormonal parameters in combination can provide an accurate assessment of MR severity and LV dysfunction in most cases. Aim of study: The aim of this study was to correlate the levels of serum NT-pro BNP with various echocardiographic parameters including 3D vena contracta width in patients with MR. Methods: 74 Patients diagnosed with primary mitral regurgitation in sinus rhythm with no conduction disturbance were included in the study. 2D and Doppler echocardiography indices were calculated. A full-volume 3D color Doppler acquisition was obtained and 3D vena contracta width was calculated and serum BNP levels were obtained. Results: NT-pro BNP levels were increased with symptoms in patients with mitral regurgitation (NYHAI: 4.48 ± 0.06, NYHAII: 5.54 ± 0.78, NYHAIII: 6.68 ± 1.21 pg/ml, $p < 0.01$). NT-pro BNP plasma levels were significantly correlated with MPI ($r = 0.945$, $p < 0.01$), and following echocardiographic indices: LVEDV ($r = 0.793$, $p < 0.01$), LVESV ($r = 0.706$, $p < 0.01$), LVEDVI ($r = 0.733$, $p < 0.01$), LVESVI ($r = 0.677$, $p < 0.01$), LVEDD ($r = 0.727$, $p < 0.01$), LVESD ($r = 0.617$, $p < 0.01$), RVSP ($r = 0.665$, $p < 0.01$), LA volume ($r = 0.735$, $p < 0.01$), LAVI ($r = 0.709$, $p < 0.01$), MR 2D VC ($r = 0.430$, $p < 0.01$), 3D VC ($r = 0.441$, $p < 0.01$), PISA ($r = 0.440$, $p < 0.01$) and negative correlation with LV ejection fraction ($r = 0.846$, $p < 0.01$), dp/dt ($r = 0.795$, $p < 0.01$), but there were no significant correlations between NT-pro BNP plasma level and LA jet area ratio ($P = 0.33$). It was observed that there was a significant correlation between 3D VC and PISA levels in patients of mitral regurgitation. However correlation is better in MR with central jet compared to eccentric jet in moderate and severe MR (r = 0.807, 0.817 vs r = 0.617, 0.572). Conclusion: This study showed that NT-pro BNP measurement has the same sensitivity and specificity as echocardiographic indices. Three-dimensional VCA may provide a reliable measurement of ROA, independent of geometric and flow assumptions.

Keywords

NT-Pro BNP, Mitral Regurgitation, Proximal Isovelocity Surface Area, Effective Regurgitant Orifice Area

1. Introduction

Mitral regurgitation (MR) is a common valvular disease that causes significant morbidity and mortality [1]. Mitral regurgitation causes progressive systolic and diastolic left ventricular dysfunction which has negative impacts on prognosis of patients with MR [2]. Understanding the degree of systolic, diastolic dysfunction and severity of regurgitation would be helpful to establish the best treatment strategy and improve patient survival [3] [4].

Accurate assessment of ventricular function and severity of MR using echocardiography alone may be difficult and bring us to diagnostic dead end. The use of multiple echocardiographic indices and hormonal parameters in combination can provide an accurate assessment of MR severity and LV dysfunction in most cases [5].

B-type natriuretic peptide and N-terminal pro BNP are synthesized and secreted in response to increase in wall stress by cardiac myocytes. Plasma levels of NT Pro BNP which are elevated in myocardial infarction and heart failure patients are independent prognostic factors in numerous studies [6] [7]. In contrast only a few studies have evaluated NT Pro BNP in valvular heart diseases [8] [9]. The purpose of this study is to compare NT Pro BNP and echocardiographic indices in patients with MR.

Accurate assessment of MR is important for clinical decision making and outcome prediction. The calculation of effective regurgitant orifice area (EROA) by the proximal isovelocity surface area (PISA) method is an important method for quantification of MR [10]. However it requires flow and geometric assumptions which has limited its clinical applications. Recently 3D echocardiography allowed for the direct measurement of the effective regurgitant orifice area by 3D guided planimetry of the vena contracta area [11]. This single measurement is not dependent on geometric and flow assumption. Therefore it can provide direct and more accurate quantification of MR than 2D measurements. The purpose of this study was also to evaluate the utility of 3D Vena contracta area in assessing the severity of MR and to correlate 3D vena contracta with 2D vena contracta and EROA.

Aim of the Study: To study the levels of NT-pro BNP and its correlation with various echocardiographic parameters including 3D vena contracta width in patients with MR. To assess the correlation between 3DVC with 2DVC and EROA.

2. Methods

2.1. Patients

The study was done prospectively in the department of cardiology, Sri Venkateswara Institute of Medical Science Tirupati, between Dec 2013 - Jan 2015. 74 patients diagnosed with primary mitral regurgitation in sinus rhythm with no conduction disturbance were included.

Patients with mitral regurgitation due to ischemic heart disease or cardiomyopathy, mitral valve stenosis, aortic valve disease, primary right heart disease, previous cardiac Surgery, arterial hypertension were excluded.

N-terminal Pro-BNP measurement: Before the performance of echocardiography, a polyethylene catheter was inserted percutaneously in a forearm vein for blood sampling and patient had been in a supine position. Samples were collected in EDTA tubes, immediately placed on ice, and transferred to the laboratory. Plasma levels of NT-pro-BNP were determined with Elecsyspro BNP analyzer (measuring range 5 - 35,000 pg/mL) using a chemiluminescent immunoassay kit (Roche Diagnostics). Detection range of the assay was 60 - 9000 pg/ml of NT-proBNP [12].

ECHO INDICES: Transthoracic M-mode, Two-dimensional and Three-dimensional color Doppler echocardiographic examinations were performed by using the Philips IE-33 machine, Holland. LV end systolic dimension (LVESD), volume (LVESV) and end diastolic volume (LVEDV) and dimension (LVEDD), ejection fraction (EF), LA volume, EROA, Vena contracta, Vena contracta width (VCW), MR jet area to left atrial area (JA/LAA) were measured as recommended by the American society of echocardiography [13] [14]. The severity of MR was graded on the basis of current recommendations as mild (<20%), moderate (20% to 39%) or severe (≥40%).

Myocardial performance index(MPI) which is defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time was calculated (normal range: 0.39 ± 0.05) as described by Tei *et al.* [15] was calculated.

2.2. Three-Dimensional Color Doppler Acquisition and Data Analysis

A full-volume 3D color Doppler acquisition was obtained with the use of the X3-1 (1 - 3 MHz) matrix array transducer from the apical window over 7 to 14 consecutive cardiac cycles with ECG gating.

The 3D color MR jet dataset was analyzed using Philips Qlab 2.0 software. Cropping was done in three different planes. The frame with the largest VCA in systole was magnified, and VCA was measured by direct planimetry of the color Doppler flow signal [16] [17].

2.3. Statistical Analysis

Data collected was analysed with IBM SPSS version 20 software. All results for continuous variables are expressed as mean ± SD. The Independent sample t-test was used for comparison of parametric variables, one-way ANOVA for comparison of values of echocardiographic indices and N-terminal pro BNP between three groups with MR. As the plasma NT-pro BNP levels were not normally distributed, logarithmic (log) transformed values were used for correlation tests. The relation between log NT-pro BNP levels and echocardiographic and hemodynamic parameters were assessed by the Pearson correlation test. The areas under the receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of NT-pro-BNP and echocardiographic variables for the prediction of abnormality of MPI (MPI of 0.45). A p value < 0.05 was considered significant.

3. Results

A total of 74 patients were included in the study. 38 (51.4%) were females. Predominant cause of MR in the present study is Chronic Rheumatic Heart Disease.

Study population is categorized into 3 groups depending on the severity of MR on 2D echocardiography. Mild MR as group I, moderate MR as group II and severe MR as group III. The baseline characteristics have been presented in **Table 1**.

Due to wide dispersion of data for NT-pro BNP levels, log NT-pro BNP levels were calculated for the three groups. Anova test was used for comparision of log NT-pro BNP levels between the three groups. There was significant correlation between severity of MR and log NT-pro BNP as shown in **Table 2**.

Log NT-pro BNP levels were significantly different ($p < 0.01$) between symptomatic severe MR (5.98 ± 0.78) and asymptomatic severe MR (4.09 ± 1.21) There was statistically significant difference in NYHA class of symptoms and log NT-pro BNP levels as shown in **Table 3**.

Correlation of log NT-pro BNP levels with echocardiographic indices is shown in **Table 4**.

NT-pro BNP plasma levels were significantly correlated with MPI ($r = 0.945$, $P < 0.01$), and following echocardiographic indices: LVEDV ($r = 0.793$, $P < 0.01$), LVESV ($r = 0.706$, $P < 0.01$), LVEDVI ($r = 0.733$, $P < 0.01$), LVESVI ($r = 0.677$, $P < 0.01$), LVEDD ($r = 0.727$, $P < 0.01$), LVESD ($r = 0.617$, $P < 0.01$), RVSP ($r = 0.665$, $P < 0.01$), LA volume ($r = 0.735$, $P < 0.01$), LAVI ($r = 0.709$, $P < 0.01$)), MR 2D VC ($r = 0.430$, $P < 0.01$), 3D VC ($r = 0.441$, $P < 0.01$) PISA ($r = 0.440$, $P < 0.01$) and negative correlation with LV ejection fraction ($r = -0.846$, $P < 0.01$), dp/dt ($r = -0.795$, $P < 0.01$), but there were no significant correlations between NT-pro BNP plasma level and LA jet area ratio ($P = 0.33$).

We categorized patients into two groups according to MPI cut off level of 0.45. It was observed that a cut off value of NT-pro BNP of 524 pg/ml predicted abnormal MPI as shown in **Figure 1**.

The sensitivity, specificity, and area under the ROC curve for abnormality of MPI by natriuretic peptide levels and echocardiographic measures are shown in Table 5.

It was observed that there was a significant correlation between 3D VC and PISA levels in patients of mitral regurgitation. However correlation is better in MR with central jet compared to eccentric jet in moderate and severe MR (r = 0.807, 0.817 vs r = 0.617, 0.572). It was observed that there was a significant correlation between 3D VC and 2D VC in all patients of mitral regurgitation with central jet and in patients of mild MR with eccentric jet. However correlation is better in central jets compared to eccentric jets in moderate MR (r = 0.956 vs r = 0.774), but there were no significant correlations between 3DVC and 2D VC in severe MR ($P = 0.27$) as shown in Table 6.

Table 1. Baseline data.

	Group 1 (Mild) n = 20	Group 2 (Moderate) n = 28	Group 3 (Severe) n = 26
MEN:WOMEN	12:8	14:14	10:16
AGE (years)	37.50 ± 13.22	46.96 ± 10.73	50.04 ± 11.60
BSA (m^2)	1.32 ± 0.07	1.43 ± 0.17	1.52 ± 0.16
LVEF (%)	60.40 ± 2.41	56.18 ± 4.23	56.73 ± 6.27
LVEDD (mm)	47.45 ± 6.05	51.29 ± 4.78	57.27 ± 3.55
LVESD (mm)	27.80 ± 3.96	32.82 ± 4.91	39.00 ± 2.89
LVEDV (ml)	100.75 ± 2.73	131.86 ± 23.15	140.50 ± 18.97
LVESV (ml)	44.20 ± 3.54	64.04 ± 9.02	68.62 ± 7.74
LVEDVI	75.90 ± 3.71	92.89 ± 22.99	92.85 ± 17.88
LVESVI	32.95 ± 2.91	44.86 ± 9.67	45.15 ± 7.95
LAVOLUME (ml)	39.65 ± 3.37	57.57 ± 6.71	65.54 ± 6.15
LAVI	29.60 ± 2.85	40.82 ± 7.99	43.12 ± 7.23
RVSP (mm of Hg)	19.10 ± 4.96	41.29 ± 8.69	50.88 ± 6.97
dp/dt (mm of Hg)	1580.50 ± 197.98	1230.89 ± 195.34	1253.23 ± 231.23
MPI	0.37 ± 0.01	0.45 ± 0.06	0.46 ± 0.09
LAJETAREA (%)	17.00 ± 1.68	32.89 ± 3.73	42.23 ± 2.21
PISA (cm^2)	0.16 ± .017	0.34 ± 0.03	0.41 ± 0.02
2DVCWIDTH (mm)	2.69 ± 0.17	6.04 ± 0.51	7.19 ± 0.19
3DVCWIDTH (mm)	2.69 ± 0.14	6.48 ± 0.79	7.56 ± 0.28

Abbreviations: LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume; LV, left ventricular; LA, left atrium; LAVI left atrial volume index, RVSP right ventricular systolic pressure, MPI-myocardial performance index, PISA proximal isovelocity surface area, VC vena contracta.

Table 2. Severity of MR and Log NT-pro BNP levels.

Diagnosis	Log NT-pro BNP levels	p - VALUE
Mild MR	4.09 ± 0.01	
Moderate MR	4.78 ± 0.79	**p < 0.01**
Severe MR	5.08 ± 1.16	

Table 3. NYHA class of symptoms and log NT-pro BNP levels.

Diagnosis	Log NT-pro BNP levels	P - VALUE
NYHA - I	4.48 ± 0.06	
NYHA- II	5.54 ± 0.78	**P < 0.01**
NYHA - III	6.68 ± 1.21	

Table 4. log NT-pro BNP levels with echocardiographic indices.

PARAMETER	r	P
LVEDV	0.793	**<0.01**
LVESV	0.706	**<0.01**
LVEDD	0.727	**<0.01**
LVESD	0. 617	**<0.01**
LVEDVI	0.733	**<0.01**
LVESVI	0.677	**<0.01**
LA volume	0.735	**<0.01**
LAVI	0.709	**<0.01**
LVEF	−0.846	**<0.01**
RVSP	0.665	**<0.01**
MPI	0.945	**<0.01**
dp/dt	−0.795	**<0.01**
2D VC WIDTH	0.430	**<0.01**
3D VC WIDTH	0.441	**<0.01**
PISA	0.440	**<0.01**
LA JET AREA RATIO	0.249	0.33

Abbreviations: LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume; LV, left ventricular; LA, left atrium; LAVI left atrial volume index, RVSP right ventricular systolic pressure, MPI-myocardial performance index, PISA proximal isovelocity surface area, VC vena contracta.

Table 5. Sensitivity, specificity and AUC for abnormality of MPI by natriuretic peptide levels and echocardiographic measures.

Variable	Cut point	Sensitivity (%)	Specificity (%)	AUC
NT-pro BNP (pg/ml)	>524	95.24	94.34	0.991
LVESV (ml)	>65	85.71	84.91	0.914
LVEDV (ml)	>127	95.24	81.13	0.947

Continued

LVESD (mm)	>34	90.48	69.81	0.854
LVEDD (mm)	>54	85.73	81.13	0.887
LA Volume (ml)	> 61	90.48	83.02	0.918
LAVI	>37	85.71	66.04	0.832
dp/dt (mm of Hg/sec)	1185	85.76	94	0.961
LVEDVI	>90	76.19	83.02	0.862
LVEF (%)	55	90.48	92.45	0.971
LVESVI	>37	97.00	54.72	0.836
RVSP (mm of Hg)	>40	98.24	69.81	0.904

Table 6. Correlations between 3DVC and PISA, 2D VC in MR.

Type of jet	Correlation of 3D VC and PISA in mild MR		Correlation of 3D VC and 2D VC in mild MR	
	Correlation coefficient	P value	Correlation coefficient	P value
Central Jet	0.959	**<0.05**	0.959	**<0.05**
Eccentric Jet	0.949	**<0.05**	0.949	**<0.05**
	Correlation of 3D VC and PISA in moderate MR		Correlation of 3D VC and 2D VC in moderate MR	
	Correlation coefficient	P value	Correlation coefficient	P value
Central Jet	0.807	**<0.05**	0.956	**<0.05**
Eccentric Jet	0.617	**<0.05**	0.774	**<0.05**
	Correlation of 3D VC and PISA in severe MR		Correlation of 3D VC and 2D VC in Severe MR	
	Correlation coefficient	P value	Correlation coefficient	P value
Central Jet	0.817	**<0.05**	0.556	**<0.05**
Eccentric Jet	0.572	**<0.05**	0.346	0.271

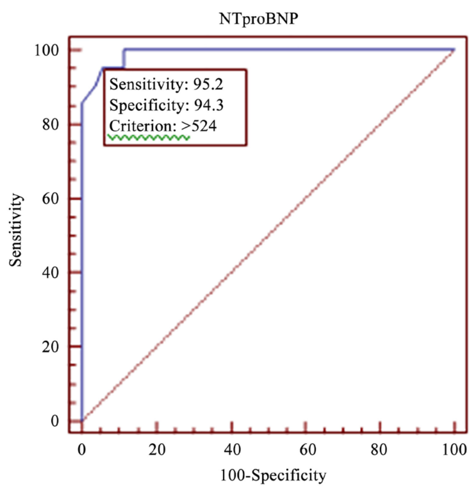

Figure 1. ROC curve for abnormality of MPI by NT-pro BNP.

4. Discussion

In our study, mitral regurgitation was almost equally distributed in both males (n = 36) and females (n = 38). We observed that Chronic Rheumatic Heart Disease was the most common cause of organic mitral regurgitation followed by MVP which was similar to that described by Kumar R *et al.* [18].

In the present study, we observed that increase in plasma NT-pro BNP levels was significantly associated with increase in severity of MR assessed by 2D and 3D echocardiography.

Similar to Yusoff R *et al.* [19] and Potocki M *et al.* [20] we found that NT-pro BNP levels were increased by symptom severity and this is concordant to other studies showing increased plasma BNP levels with higher NYHA classes. Symptomatic patients were more likely to have more severe MR. These observations suggest that natriuretic peptide levels provide an additional method for assessing the severity and symptoms of MR when the LVEF is normal and for monitoring disease progression. Natriuretic peptides reflect cardiac stress and therefore NT-pro-BNP may be helpful in the clinical evaluation and management of patients with MR, especially when it is doubtful whether symptoms are related to MR or not.

We observed that in addition to associations with echocardiographic measures of the severity of MR, natriuretic peptide levels were higher in symptomatic than in asymptomatic patients with severe MR.

Similar to Detaint *et al.* [21], Shokoufeh Hajsadeghi *et al.* [22] we observed that NT-pro BNP levels correlate with left ventricular volumes and dimensions both in systole and diastole, left atrial volume and right ventricular systolic pressure. We also observed significant negative correlation of NT-pro BNP with left ventricular ejection fraction. In this context, NT-pro BNP activation should direct the attention of clinicians toward more severe LA, LV, and hemodynamic consequences. Such patients should be evaluated carefully, and additional quantitative and hemodynamic measurements may be indicated.

Left ventricular ejection fraction is an important determinant in mitral valve surgery in patients with mitral regurgitation, but in some instances it is difficult to accurately measure LVEF because of abnormally shaped ventricles or poorly defined endocardium. Myocardial performance index, a Doppler-derived echocardiographic index, is independent of ventricular geometry, blood pressure and age. Since MPI incorporates both systolic and diastolic ventricular function, may provide a better assessment of the global LV function than LVEF. Similar to Shokoufeh Hajsadeghi *et al*., Sayar N *et al.* [23] in the present study, we observed that MPI correlates positively with left ventricular volumes and dimensions both in systole and diastole, RVSP, LA volume. Similar to Kargin R *et al.* [24] in our study correlations were identified between the MPI and plasma NT-pro BNP level and severity of MR. Correlation of MPI and dp/dt may indirectly describe parallel relation between dp/dt and isovolumic contraction time. These findings supports the previous studies which believed in patients with mitral regurgitation, NT-pro BNP activation is a result of alterations in hemodynamic, atrial and ventricular status rather than the degree of regurgitation alone. MPI may be considered as a new echocardiographic parameter for the assessment of global ventricular function in mitral regurgitation.

When we have chosen cut point level of 0.45 for MPI based on Ono M *et al.* [25] we could define a cutoff value of 524 pg/ml for NT-pro BNP serum level and some of the echocardiographic indices to differentiate normal and abnormal MPI.

Furthermore, calculation and comparison of area under ROC curves for NT-pro BNP and echocardiographic measures such as LV end-diastolic volume, LV end-systolic volume, LV end-systolic dimension and LV end-diastolic dimension showed that there is no significant difference between these indices such that one may be chosen as the best one for prediction of MPI abnormality. Results of this study suggest that natriuretic peptide testing may add to the information obtained by echocardiography in the assessment of MR in clinical practice. When echocardiographic assessment is technically difficult, low NT-pro BNP levels would suggest that MR is not severe. Measurement of natriuretic peptides may also be useful when it is not clear whether symptoms of dyspnea or fatigue are due to cardiac disease.

Similar to Iwakura *et al.* [26], Kahlert *et al.* [27] in our study we observed that there was a significant correlation between 3D VC and PISA levels in patients of mitral regurgitation, however correlation is better in MR with central jet compared to eccentric jet in moderate and severe MR ($r = 0.807$, 0.817 vs $r = 0.617$, 0.572). We also observed that there was a significant correlation between 3D VC and 2D VC in all patients of mitral regurgitation with central jet and in patients of mild MR with eccentric jet. However correlation is better in central jets compared to eccentric jets in moderate MR ($r = 0.956$ vs $r = 0.774$) similar to Xin Zeng *et al.* [28]. Similar to Chaim Yosefy *et al.* [29] we observed that for eccentric jets, VC width by 2D echo was correlated less well with 3D VC, and 2D VC width underestimated regurgitant orifice area especially in moderate to severe MR patients. Accurate assessment of MR is important but still challenging in daily clinical practice. Currently, various color Doppler 2D methods are used for MR quantification, however, each method has its limitations, based on technical issues or inaccurate geometric assumption. Besides the 2D methods, recent studies showed that planimetry of the VCA was highly feasible by using color Doppler 3D echocardiography, which provided a new approach for MR quantification by direct measurement of the ROA. Although no gold standard is available for comparison, this result supports the previous finding of the advantages of 3D VCA in assessing eccentric MR jets compared with 2D methods.

5. Limitations

Sample size is small and no follow up was done. Present study suggests that a single baseline measurement does not reliably predict disease progression, serial measurements may be useful. Exercise stress echocardiography to identify LV dysfunction with a maintained resting EF was not done.

6. Conclusion

This study showed that NT-pro BNP measurement has the same sensitivity and specificity as echocardiographic indices and may be used as a hormonal factor for the evaluation of patients with mitral regurgitation in combination with echocardiography. Myocardial performance index combined with NT-proBNP measurement may be helpful in detection of subclinical impairments in left ventricle functions. Three-dimensional VCA may provide a single, directly visualized, and reliable measurement of ROA, independent of geometric and flow assumptions, which classifies MR severity comparable to current clinical practice using the ASE-recommended 2D integrative method.

References

[1] Nkomo, V.T., Gardin, J.M., Skelton, T.N., Gottdiener, J.S., Scott, C.G. and Enriquez-Sarano, M. (2006) Burden of Valvular Heart Diseases: A Population-Based Study. *Lancet*, **368**, 1005-1011. https://doi.org/10.1016/S0140-6736(06)69208-8

[2] Jones, E.C., Devereux, R.B., Roman, M.J., Liu, J.E., Fishman, D., Lee, E.T., et al. (2001) Prevalence and Correlates of Mitral Regurgitation in a Population-Based Sample (The Strong Heart Study). *American Journal of Cardiology*, **87**, 298-304. https://doi.org/10.1016/S0002-9149(00)01362-X

[3] Singh, J.P., Evans, J.C., Levy, D., Larson, M.G., Freed, L.A., Fuller, D.L., *et al.* (1999) Prevalence and Clinical Determinants of Mitral, Tricuspid, and Aortic Regurgitation (The Framingham Heart Study). *American Journal of Cardiology*, **83**, 897-902. https://doi.org/10.1016/S0002-9149(98)01064-9

[4] Eckberg, D.L., Gault, J.H., Bouchard, R.L., Karliner, J.S. and Ross Jr., J. (1973) Mechanics of Left Ventricular Contraction in Chronic Severe Mitral Regurgitation. *Circulation*, **47**, 1252-1259. https://doi.org/10.1161/01.CIR.47.6.1252

[5] Watanabe, M., Murakami, M., Furukawa, H. and Nakahara H. (2004) Is Measurement of Plasma Brain Natriuretic Peptide Levels a Useful Test to Detect for Surgical Timing of Valve Disease. *International Journal of Cardiology*, **96**, 21-24. https://doi.org/10.1016/j.ijcard.2003.07.009

[6] Seino, Y., Ogawa, A., Yamashita, T., *et al.* (2004) Application of NT-pro BNP and BNP Measurements in Cardiac Care: A More Discerning Marker for the Detection and Evaluation of Heart Failure. *European Journal of Heart Failure*, **6**, 295-300. https://doi.org/10.1016/j.ejheart.2003.12.009

[7] Levin, E.R., Gardner, D.G. and Samson, W.K. (1998) Natriuretic Peptides. *The New England Journal of Medicine*, **339**, 321-328. https://doi.org/10.1056/NEJM199807303390507

[8] Cheung, B.M. and Kumana, C.R. (1998) Natriuretic Peptides—Relevance in Cardiovascular Disease. *JAMA*, **280**, 1983-1984. https://doi.org/10.1001/jama.280.23.1983

[9] Mark Richards, A., Gary Nicholls, M., Yandle, T.G., Frampton, C., Espiner, E.A., Turner, J,G., *et al.* (1998) Plasma N-Terminal Probrain Natriuretic Peptide and Adrenomedullin—New Neurohormonal Predictors of Left Ventricular Function and Prognosis after Myocardial Infarction. *Circulation*, **97**, 1921-1929. https://doi.org/10.1161/01.CIR.97.19.1921

[10] Enriquez-Sarano, M., Miller Jr., F.A., Hayes, S.N., Bailey, K.R., Tajik, A.J. and Seward, J.B. (1995) Effective Mitral Regurgitant Orifice Area: Clinical Use and Pitfalls of the Proximal Isovelocity Surface Area Method. *Journal of the American College of Cardiology*, **25**, 703-709. https://doi.org/10.1016/0735-1097(94)00434-R

[11] Lesniak-Sobelga, A., Olszowska, M., Pienazek, P., Podolec, P. and Tracz, W. (2004) Vena Contracta width as a Simple Method of Assessing Mitral Valve Regurgitation. Comparison with Doppler Quantitative Methods. *The Journal of Heart Valve Disease*, **13**, 608-614.

[12] Colburn, W., De Gruttola, V.G., De Mets, D.L., *et al*. (2001) Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework. *Clinical Pharmacology and Therapeutics*, **69**, 89-95. https://doi.org/10.1067/mcp.2001.113989

[13] Lang, R.M., Bierig, M., Devereux, R.B., Flachskampf, F.A., Foster, E., Pellikka, P.A., Picard, M.H., Roman, M.J., Seward, J., Shanewise, J.S., Solomon, S.D., Spencer, K.T., Sutton, M.S. and Stewart, W.J. (2005) Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. *Journal of the American Society of Echocardiography*, **18**, 1440-1463. https://doi.org/10.1016/j.echo.2005.10.005

[14] Zoghbi, W.A., Enriquez-Sarano, M., Foster, E., Grayburn, P.A., Kraft, C.D., Levine, R.A., *et al*. (2003) Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-Dimensional and Doppler Echocardiography. *Journal of the American Society of Echocardiography*, **16**, 777-802. https://doi.org/10.1016/S0894-7317(03)00335-3

[15] Tei, C. (1995) New Non-Invasive Index for Combined Systolic and Diastolic Ventricular Function. *Journal of Cardiology*, **26**, 135-136.

[16] Little, S.H., Pirat, B., Kumar, R., *et al*. (2008) Three-Dimensional Color Doppler Echocardiography for Direct Measurement of Vena Contracta Area in Mitral Regurgitation: *In Vitro* Validation and Clinical Experience. *JACC Cardiovascular Imaging*, **1**, 695-704. https://doi.org/10.1016/j.jcmg.2008.05.014

[17] Nanda, N.C., Kisslo, J., Lang, R., Pandian, N., Marwick, T., *et al*. (2004) Examination Protocol for Three Dimensional Echocardiography. *Echocardiography*, **21**, 763-768.

[18] Kumar, R., Sinha, N., Ahuja, R.C., Saran, R.K., Dwivedi, S.K. and Suri, A. (1993) Etiology of Isolated Mitral Regurgitation: A Clinico-Echocardiographic Study. *Indian Heart Journal*, **45**, 173-178.

[19] Yusoff, R., Clayton, N., Keevil, B., Morris, J. and Ray, S. (2006) Utility of Plasma N-Terminal Brain Natriuretic Peptide as a Marker of Functional Capacity in Patients with Chronic Severe Mitral Regurgitation. *American Journal of Cardiology*, **97**, s1498-s1501. https://doi.org/10.1016/j.amjcard.2005.11.085

[20] Potocki, M., Mair, J., Weber, M., Hamm, C., Burkard, T., Hiemetzberger, R., *et al*. (2009) Relation of N-Terminal Pro-B-Type Natriuretic Peptide to Symptoms, Severity, and Left Ventricular Remodeling in Patients with Organic Mitral Regurgitation. *American Journal of Cardiology*, **104**, 559-564. https://doi.org/10.1016/j.amjcard.2009.04.023

[21] Detaint, D., Messika-Zeitoun, D., Avierinos, J.F., Scott, C., Chen, H., Burnett, J.C., *et al*. (2005) B-Type Natriuretic Peptide in Organic Mitral Regurgitation: Determinants and Impact on Outcome. *Circulation*, **111**, 2391-2397. https://doi.org/10.1161/01.CIR.0000164269.80908.9D

[22] Hajsadeghi, S., Samiei, N., Moradi, M., Majid, M., Kashani, L., Amani, A., *et al*. (2010) Comparison of N-Terminal pro B-Natriuretic Peptide and Echocardio-

graphic Indices in Patients with Mitral Regurgitation. *Clinical Medicine Insights*: *Cardiology*, **4**, 111-116. https://doi.org/10.4137/CMC.S6062

[23] Sayar, N., Lütfullah Orhan, A., Cakmak, N., Yilmaz, H., Atmaca, H., Tangürek, B., *et al*. (2008) Correlation of the Myocardial Performance Index with Plasma B-Type Natriuretic Peptide Levels in Patients with Mitral Regurgitation. *The International Journal of Cardiovascular Imaging*, **24**, 151-157. https://doi.org/10.1007/s10554-007-9237-5

[24] Kargin, R., Esen, O., Akçakoyun, M., Pala, S., Candan, O., Omaygenç, M.O., *et al*. (2010) Relationship between the Tissue Doppler-Derived Tei Index and Plasma Brain Natriuretic Peptide Levels in Patients with Mitral Regurgitation. *The Journal of Heart Valve Disease*, **19**, 35-42.

[25] Ono, M., Kazuaki, T., Asanuma, T., *et al*. (2001) Doppler Echocardiography Derived Index of Myocardial Performance: Comparison with Brain Natriuretic Peptide Levels in Various Heart Disease. *Japanese Circulation Journal*, **65**, 637-642. https://doi.org/10.1253/jcj.65.637

[26] Iwakura, K., Ito, H., Kawano, S., *et al*. (2006) Comparison of Orifice Area by Transthoracic Three-Dimensional Doppler Echocardiography versus Proximal Isovelocity Surface Area (PISA) Method for Assessment of Mitral Regurgitation. *American Journal of Cardiology*, **97**, 1630-1637. https://doi.org/10.1016/j.amjcard.2005.12.065

[27] Kahlert, P., Plicht, B., Schenk, I.M., Janosi, R.A., Erbel, R. and Buck, T. (2008) Direct Assessment of Size and Shape of Noncircular Vena Contracta Area in Functional versus Organic Mitral Regurgitation Using Real-Time Three-Dimensional Echocardiography. *Journal of the American Society of Echocardiography*, **21**, 912-921. https://doi.org/10.1016/j.echo.2008.02.003

[28] Zeng, X., Levine, R.A., Hua, L., Morris, E.L., Kang, Y., Flaherty, M., *et al*. (2011) Diagnostic Value of Vena Contracta Area in the Quantification of Mitral Regurgitation Severity by Color Doppler 3D Echocardiography. *Circulation*: *Cardiovascular Imaging*, **4**, 506-513. https://doi.org/10.1161/CIRCIMAGING.110.961649

[29] Chaim, Y., Judy, H., Sarah, C., Mordehay, V., Thanh-Thao, T.-N., Mark, D., *et al*. (2009) Direct Measurement of Vena Contract a Area by Real-Time 3-Dimensional Echocardiography for Assessing Severity of Mitral Regurgitation. *American Journal of Cardiology*, **104**, 978-983. https://doi.org/10.1016/j.amjcard.2009.05.043