THE RELATIONSHIP BETWEEN TISSUE DOPPLER PARAMETERS AND SERIC NTPROBNP LEVELS IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

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ABSTRACT

Introduction: Tissue Doppler imaging (TDI) is a novel echocardiographic technique that permits measurements of mitral annular and myocardial velocities. The global myocardic index determined by the pulsed Doppler method (GMI) is a simple and noninvasive measurement for assessing global left ventricular (LV) function. This index can also be obtained by TDI (GMI-TDI). N-terminal pro-brain natriuretic peptide (NTproBNP) is recognized as a reliable marker of systolic and diastolic LV function. Aim: To assess the relationship between different TDI parameters and NTproBNP levels in patients with left ventricular dysfunction, in sinus rhythm. Material and methods: Conventional echocardiography and TDI were performed simultaneously with NTproBNP determination in 137 consecutive patients with left ventricular dysfunction, in sinus rhythm, referred for echocardiography. Patients with inadequate echocardiographic image, paced rhythm, severe mitral valvular disease, mitral prosthesis, pericardial disease, acute coronary syndrome, coronary artery by-pass within 72 hours or renal failure were excluded. The remaining 110 patients (age 63 ±13 years) formed our study group. Peak early diastolic transmitral velocity (E, using pulsed Doppler) / peak early mitral annular diastolic velocity (Ea, using TDI) ratio and the optimal GMI-TDI cut-off for prediction of NTproBNP levels >900 pg/ml was used.

Results: Simple regression analysis demonstrated a significant linear correlation between GMI-TDI and NTproBNP (r=0.51, p<0.001). Significant but weaker correlations were found between NTproBNP and E/Ea (r=0.56, p<0.001), pulmonary artery systolic pressure (r=0.53, p<0.001), mitral E deceleration time (r=0.30, p=0.002) and the duration of the systole Sa-wave (r=-0.24, p=0.01). We couldn’t demonstrate significant relationships between NTproBNP and left atrial diameter, left atrial surface or left atrial volume. The optimal GMI-TDI cut-off for prediction of NTproBNP levels >900 pg/ml was 0.51 (sensitivity of 82% and specificity of 80%) with 90% accuracy. Conclusions: GMI-TDI had a good correlation with plasma NTproBNP levels and can be used with good accuracy for the assessment of the LV function.

Key Words: Natriuretic Peptide, Global Myocardial Index, Mitral Annulus Velocity, Tissue Doppler Imaging

INTRODUCTION

Tissue Doppler imaging (TDI) is a novel echocardiographic technique that permits measurements of mitral annular and myocardic velocities.1 The ratio between early diastolic transmitral velocity (E - measured by pulsed Doppler echocardiography) and
early mitral annular diastolic velocity (Ea - measured by pulsed TDI) has been demonstrated to correlate with left ventricular (LV) filling pressure.\textsuperscript{1,2} E/Ea is currently used for the noninvasive assessment of LV filling pressure. However, this parameter may be inaccurate in some categories of patients (particularly in patients with E/Ea ratio between 8 and 15).\textsuperscript{3}

N-terminal pro-brain natriuretic peptide (NTproBNP) has been used for the noninvasive assessment of LV function.\textsuperscript{4} Increased levels of NTproBNP are produced mainly in response to LV wall pressure and volume overload, and invasive studies have demonstrated that elevated natriuretic peptides correlate well with increased LV filling pressures.\textsuperscript{5,6} It is reported that elevated levels of natriuretic peptides are strongly related to symptoms, cardiac events and mortality.\textsuperscript{3} A value of <900 pg/ml was recently recommended in the PRIDE study (NTproBNP Investigation of Dyspnea in the Emergency Department) as cut-off to “rule out” heart failure with 94% negative predictive value.\textsuperscript{6,7} The relationship between natriuretic peptides and TDI velocities (Ea, E/Ea) is still subject of debate.\textsuperscript{8-10}

This study was designed to evaluate the correlation between the different tissue Doppler parameters and the plasma NTproBNP levels in consecutive patients with LV dysfunction, in sinus rhythm, referred for echocardiography.

MATERIAL AND METHODS

Patients
We screened 137 consecutive patients with LV dysfunction (according to European Association of Echocardiography/American Society of Echocardiography recommendations), in sinus rhythm, referred for echocardiography.\textsuperscript{11} Patients with inadequate echocardiographic image, congenital heart disease, paced rhythm, severe mitral valvular disease, mitral prosthesis, pericardial disease, acute coronary syndrome, coronary artery by-pass within 72 hours or renal failure were excluded. The remaining 110 patients formed our study group. All the patients gave informed consent in agreement with ethics regulations.

Echocardiography and Doppler
Conventional echocardiography and TDI were performed simultaneously with NTproBNP determination. Two-dimensional and Doppler echocardiographic examinations were performed with an ultrasonographic system (Vivid 7 General Electric, Milwaukee, WI) equipped with a multifrequency transducer. Two-dimensional and M-mode measurements were performed according to the recommendations of the American Society of Echocardiography, working together with the European Association of Echocardiography.\textsuperscript{12} Transmitral flow patterns were recorded from apical four-chamber windows with a 3-5 mm pulsed-sample Doppler volume placed between mitral valve tips in diastole during five consecutive cardiac cycles. Care was taken to obtain the smallest possible angle between the direction of transmural flow and the ultrasound beam. Mitral inflow measurements (at end expiration) included peak early velocity (E), peak late velocity (A), E/A ratio, and E wave deceleration time.\textsuperscript{13} Parameters were recorded for five consecutive cardiac cycles, and results were averaged. Pulsed Doppler signals were recorded at a horizontal sweep of 100 mm/s. Measurement of systolic pulmonary artery pressure was performed using the maximal regurgitant velocity at the tricuspid valve by continuous Doppler.\textsuperscript{15}

Figure 1. Bedside measurements of spectral Doppler peak early transmitral inflow (E) velocity (panel a) and spectral tissue Doppler peak early diastolic (Ea) velocities, respectively peak systolic (Sa) velocities, at the medial (panel b) and lateral (panel c) corners of mitral annulus. The average of the velocities from medial and lateral mitral annulus was used to calculate the E/Ea ratio.

Tissue Doppler Measurements
The tissue Doppler program was set in pulsed-wave Doppler mode. Motion of mitral annulus was recorded in the apical four-chamber view at a frame rate of 80 to 140 frames per second.\textsuperscript{14} A 3-5 mm sample volume was positioned sequentially at the lateral and septal corners of the mitral annulus. Two major negative velocities were recorded with the movement of the annulus toward the base of the heart during diastole: one during the early phase of diastole (Ea), and another during the late phase of diastole (Aa). A major positive systolic velocity was recorded with the movement of the annulus toward
the cardiac apex during systole. The peak myocardial systolic velocity was defined as the maximum velocity during systole, excluding the isovolumic contraction (Sa). All velocities were recorded for five consecutive cardiac cycles at end expiration, and results were averaged. All tissue Doppler signals were recorded at horizontal time sweep set at 100 mm/s. E/Ea ratio was calculated; the average of the velocities of septal and lateral mitral annulus was used. (Fig. 1) From TDI recordings, the time interval during diastole (a') and the duration of the systole Sa-wave (b') were measured. (Fig. 2) The global myocardial index determined by TDI (GMI-TDI) was calculated as (a'-b')/b'. GMI-TDI was measured at the septal and lateral sites of the mitral annulus, and the average was utilized. All measurements were performed by two experienced echocardiographers blinded to the NTproBNP levels.

**NT-proBNP measurement**

NT-proBNP levels were measured in blood samples collected by venipuncture into EDTA tubes, within 30 minutes before or after echocardiography. The automated electrochemiluminescence immunoassay (Roche-Elecsys 2010) was used. The measuring range, defined by the lower detection limit and the maximum of the master curve, provided by the manufacturer was 5 to 35 000 pg/ml.

**Statistics**

Data are presented as mean value ± standard variation (SD). Correlation between NTproBNP and echocardiographic parameters was determined by Pearson’s correlation coefficient. Receiver operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity. All statistical analyses used the software package SPSS version 11.5 (SPSS Inc, Chicago, II, USA). A p value of <0.05 was accepted as statistically significant.

**RESULTS**

The current study included 110 consecutive patients (mean age: 63 ± 13 years; 52 women) with LV dysfunction, in sinus rhythm, referred for echocardiography. The admitting diagnoses were coronary artery disease (68 patients), nonischemic cardiomyopathy (27 patients), systemic hypertension (10 patients), valvular disease (aortic regurgitation - 4 patients) and ascending aortic aneurysm (one patient). Characteristics of the study group are presented in Table 1. TDI mitral annular velocities were recordable at both sites of the mitral annulus in all patients.

**Table 1.** Baseline characteristics of the study group [data are presented as mean ± SD or No. (%)].

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
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<tbody>
<tr>
<td>Mean age, years</td>
<td>63±13</td>
</tr>
<tr>
<td>Female/male gender</td>
<td>52(47) / 58(53)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 4.6</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>99 ± 12.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>68 (62)</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>27 (24.5)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Valvular dysfunction</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Ascending aortic aneurysm</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>40 ± 14</td>
</tr>
<tr>
<td>Ea, cm/s</td>
<td>7.1 ± 2.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>21</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.7</td>
</tr>
<tr>
<td>Sa, cm/s</td>
<td>6.5 ± 2.4</td>
</tr>
<tr>
<td>Maximum</td>
<td>17</td>
</tr>
<tr>
<td>Minimum</td>
<td>3.1</td>
</tr>
<tr>
<td>E/Ea</td>
<td>11.5 ± 4.1</td>
</tr>
<tr>
<td>Maximum</td>
<td>25.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>3.1</td>
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<tr>
<td>GMI-TDI</td>
<td>0.58 ± 0.27</td>
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<tr>
<td>Maximum</td>
<td>1.19</td>
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<tr>
<td>Minimum</td>
<td>0.19</td>
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<tr>
<td>PASP, mmHg</td>
<td>41.9±14.9</td>
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<tr>
<td>Maximum</td>
<td>85</td>
</tr>
<tr>
<td>Minimum</td>
<td>14</td>
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<tr>
<td>NTproBNP, pg/ml</td>
<td>3055±4011</td>
</tr>
<tr>
<td>Maximum</td>
<td>25900</td>
</tr>
<tr>
<td>Minimum</td>
<td>20</td>
</tr>
<tr>
<td>NTproBNP &gt; 900 pg/ml</td>
<td>66(60)</td>
</tr>
</tbody>
</table>

LV = left ventricle; E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity ; GMI-TDI = global myocardial index obtained by Tissue Doppler Imaging; NTproBNP = N-terminal pro-brain natriuretic peptide; PASP = pulmonary artery systolic pressure; Sa = maximal systolic velocity of mitral annulus.
Simple regression analysis demonstrated a statistically significant linear correlation between GMI-TDI and NTproBNP levels ($r=0.73$, $p<0.001$). (Fig. 3a) This was superior to the classical E/Ea correlation ($r=0.56$, $p<0.001$). Significant correlations were also found between NTproBNP levels and Sa ($r=-0.43$, $p<0.001$), Ea ($r=-0.24$, $p=0.01$), pulmonary artery systolic pressure ($r=0.53$, $p<0.001$), mitral E/A ratio ($r=0.42$, $p=0.001$), E wave ($r=0.33$, $p<0.001$), mitral E deceleration time ($r=-0.30$, $p=0.001$) and LVEF ($r=-0.26$, $p=0.006$). (Fig. 3c) We couldn’t demonstrate significant relationships between NTproBNP and left atrial diameter, left atrial surface, left atrial volume, indexed left atrial volume or end-diastolic LV volume.

The area under ROC-curve (AUC) for prediction of NTproBNP levels $>900$ pg/ml was greatest for GMI-TDI (AUC=0.90, $p<0.001$), followed by E/Ea ratio (AUC=0.76, $p<0.001$) and pulmonary artery systolic pressure (AUC=0.75, $p<0.001$). A statistical comparison of the ROC curves demonstrates significant differences between GMI-TDI and E/Ea ($p=0.001$), and between TDI-GMI and pulmonary artery systolic pressure ($p<0.001$), respectively. (Fig. 4)

The optimal GMI-TDI cut-off for prediction of NTproBNP levels $>900$ pg/ml was 0.51 (sensitivity of 82%, specificity of 80%). In comparison, an optimal E/Ea cut-off value of 10.5 had a sensitivity of 74% and a specificity of 73%, respectively a cut-off value of 38 mmHg for pulmonary artery systolic pressure had a sensitivity of 73% and specificity of 70%.

The GMI-TDI showed a better correlation with NTproBNP in patients with normal LV ejection fraction (EF $\geq$50%) (34 patients, 31%, $r=0.76$, $p<0.001$) compared with those with depressed LVEF (76 patients, 69%, $r=0.69$, $p<0.001$).
Figure 5. Scatter plot of the relationship between global myocardial index determined by Tissue Doppler Imaging (GMI-TDI) (first panel), Sa (second panel) and N-terminal pro-brain natriuretic peptide (NTproBNP) in patients with E/Ea between 8 and 15. E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity; Sa = maximal systolic velocity of mitral annulus.

Mitral E/Ea between 8 and 15

Because intermediate E/Ea ratio (between 8 and 15) is an obscure zone for the estimation of LV filling pressure, this group was analyzed separately (60 patients, 54%). In these patients, NTproBNP was better correlated with GMI-TDI (r = 0.61, p < 0.001) than with Sa (r = -0.50, p < 0.001), pulmonary artery systolic pressure (r = 0.42, p = 0.001) or E/Ea ratio (r = 0.30, p = 0.03). (Fig 5) The areas under the ROC curves for prediction of NTproBNP levels >900 pg/ml were 0.84 for GMI-TDI (p = 0.001), 0.74 for pulmonary artery systolic pressure (p = 0.002), 0.70 for E/Ea ratio (p = 0.008), and 0.67 for Sa (p = 0.02). (Fig 6) A statistical comparison of the ROC curves demonstrates significant differences between GMI-TDI and Sa (p = 0.008), and between GMI-TDI and pulmonary artery systolic pressure (p = 0.002), respectively. The optimal cut-off value for E/(Ea×Sa) ratio was also 0.51 had a sensitivity of 76% and specificity of 73% for predicting NTproBNP levels >900 pg/ml.

DISCUSSION

In the present study we analyzed the correlation between different tissue Doppler parameters and NTproBNP plasma levels in consecutive patients with LV dysfunction, in sinus rhythm, referred for echocardiography. The GMI-TDI performed better than other standard echocardiographic and tissue Doppler parameters in predicting high NTproBNP plasma levels.

Data on the association between conventional echocardiographic parameters and plasma levels of natriuretic peptides are contradictory. Previous studies have shown a correlation between natriuretic peptides and septal thickness, LV end-diastolic diameter, LVEF, left atrial diameter, and maximal tricuspid regurgitant flow velocity. In these studies no correlation has been demonstrated between natriuretic peptides and other echocardiographic and Doppler parameters: E/A ratio, mitral E deceleration time, E wave or left atrial surface. We report significant correlations but with a relatively low correlation coefficient between NTproBNP levels and E/A ratio, E velocity, LV ejection fraction and E deceleration time.

We did not find significant relationships between NTproBNP and left atrial diameter, left atrial surface, left atrial volume, indexed left atrial volume or end-diastolic LV volume.

The relationship between natriuretic peptides and TDI velocities (Ea, Sa, E/Ea) is controversial. Mottram et al did not find a correlation between Ea and BNP levels in hypertensive patients. However, these
authors reported a moderate relationship between late diastolic mitral annular velocity and BNP.

In a study performed by Tretjak et al, Ea was the best predictor of the NTproBNP levels in patients with heart failure irrespective of rhythm or LV systolic function. In that study Sa was notably correlated with NTproBNP. These data are in agreement with our study, where Sa and Ea had a significant but low correlations with NTproBNP levels. This difference can probably be explained by differences in inclusion criteria: we studied consecutive patients with LV dysfunction, in sinus rhythm, while over 60% of heart failure patients in the study by Tretjak et al were in atrial fibrillation. Mottram et al restricted their analysis to hypertensive patients in sinus rhythm and normal LVEF.

E/Ea ratio is actually used for estimating LV filling pressure. In our study, the E/Ea ratio showed a moderate correlation with NTproBNP levels. Ceyhan and Troughton observed also significant relationships between BNP levels and E/Ea ratio; results which disagree with another study reporting a weak correlation between E/Ea ratio and NTproBNP levels.

Myocardial performances index (GMI), defined as the sum of isovolumetric contraction and relaxation durations divided by ejection time and reflecting a combined LV systolic and diastolic function, was proposed by Tei. This index has been demonstrated to be a powerful and independent prognostic indicator in patients with various cardiac disorders. This index can also be obtained by TDI (GMI-TDI).

GMI obtained from tissue Doppler echocardiography has an inherent advantage of recording its systolic and diastolic components simultaneously on the same cardiac cycle. In a recent study, Su et al observed that GMI-TDI increased with worsening of LV diastolic function and can effectively identify the pseudonormal/restrictive mitral inflow pattern. The present study demonstrates for the first time that GMI-TDI provides a close prediction of NTproBNP. In our series, the GMI-TDI appears to be more accurate than the classical E/Ea index for the estimation of NTproBNP levels in patients in sinus rhythm. The optimal cut-off value for prediction of NTproBNP levels >900 pg/ml was 0.51. In the present study, GMI-TDI correlated well with levels of NTproBNP regardless of LVEF. GMI-TDI index is a marker of LV diastolic and systolic function and reflects LV filling pressure. Hence, GMI-TDI index can provide a simple and feasible method in assessing the global LV myocardial performance.

Moreover, the advantage of this index is its components derived from the same cardiac cycle and beat-to-beat variations can be avoided. NTproBNP is also recognized as a reliable marker of both systolic and diastolic ventricular function.

Ommen et al and Dokainish et al suggested that E/Ea between 8 and 15 is unreliable for the prediction of LV filling pressure. In our subgroup of patients with E/Ea between 8 and 15, GMI-TDI showed a better correlation with NTproBNP compared to the classic E/Ea and other studied echocardiographic parameters. As in the overall group, a cut-off of 0.51 for GMI-TDI had a good sensitivity and specificity for detecting NTproBNP >900 pg/ml in patients with E/Ea between 8 and 15. This cut-off can be used in clinical practice to predict high levels of plasma NTproBNP.

The E/Ea ratio was superior to other echocardiographic parameters in predicting survival in patients with myocardial infarction. The value of GMI-TDI as a predictor of survival is to be established by further studies in subsets of patients with normal and impaired LV function.

Limitations

The number of patients in this study was relatively small; however, we were able to reach several significant observations. A high proportion of patients referred for echocardiography in our laboratory have cardiac diseases. We deliberately did not use more sophisticated Doppler parameters, such as pulmonary venous curves or mitral inflow during a Valsalva maneuver, as these Doppler parameters are difficult to record and thus not suitable for simple screening. We have limited the tissue Doppler measurements at two sites (septal and lateral mitral annulus) and we did not examine anterior and posterior velocities that might have provided additional information.

Patients with atrial fibrillation/flutter, inadequate echocardiographic image, congenital heart disease, paced rhythm, severe mitral valvular disease, mitral prosthesis, pericardial disease, acute coronary syndrome, coronary artery by-pass within 72 hours or renal failure were not included. Our results must be taken with caution in these subsets of patients.

It is well recognized that the levels of NTproBNP are influenced by body mass index. In the Framingham Heart Study higher body mass index was associated with lower natriuretic peptide levels. A substudy from PRIDE demonstrated a slight reduction in overall diagnostic accuracy with NTproBNP in obese patients. In our study, the mean body mass index was comparable to the published values.
CONCLUSIONS

GMI-TDI strongly correlates with plasma NTproBNP levels, regardless of LV ejection fraction, and can be a simple and accurate echocardiographic index in patients with LV dysfunction, in sinus rhythm. Moreover it proves to be reliable particularly in patients with E/Ea between 8 and 15. The optimal E/(Ea×Sa) cut-off of 0.51 has a good sensitivity and specificity and can be used in clinical practice for the noninvasive assessment of the LV function.

REFERENCES