THE ROLE OF TISSUE DOPPLER ECHOCARDIOGRAPHY IN THE ESTIMATION OF NTPROBNP LEVEL IN PATIENTS WITH DILATED CARDIOMIOPATHY

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ABSTRACT

Introduction: N-terminal pro-brain natriuretic peptide (NTproBNP) correlates with left ventricular (LV) filling pressure. The ratio between early diastolic transmitral velocity and early mitral annular diastolic velocity (E/Ea) reflects LV filling pressure in a variety of cardiac diseases. Aim: To assess the relationship between a new echocardiographic parameter, E/(EaxSa), where Sa is the maximal systolic velocity of mitral annulus, and NTproBNP in patients with dilated cardiomyopathy (DCM). Material and methods: Fifty-eight consecutive patients (age 63±13 years) with DCM, in sinus rhythm, referred for echocardiography, were analyzed simultaneously with NTproBNP. No patients were having inadequate echocardiographic images, paced rhythm, mitral prosthesis, severe mitral annular calcification or renal failure. E/Ea and E/(EaxSa) were assessed by conventional echocardiography and tissue Doppler imaging of lateral and medial mitral annulus. The average of the velocities from the medial and lateral site was used. Results: A statistically significant linear correlation was found between E/(EaxSa) and NTproBNP (r = 0.73, p < 0.0001). Significant correlations were also found between NTproBNP and E/Ea (r = 0.49, p = 0.001), Sa (r = -0.47, p < 0.001), Ea (r = -0.40, p = 0.001), E (r = 0.34, p < 0.001), and mitral E deceleration time (r = -0.36, p = 0.005). Conclusions: E/(EaxSa) correlates strongly with plasma NTproBNP level and can be a simple, reproducible and accurate echocardiographic index in patients with DCM in sinus rhythm.

INTRODUCTION

Dilated cardiomyopathy (DCM) is the most frequent form of non-ischemic cardiomyopathy; the cavity of the heart is enlarged and stretched (cardiac dilation) causing the heart to become weak and not pump normally.1 Because the number of patients with DCM is increasing, new and more efficient diagnostic modalities (other than conventional echocardiography and radionuclide ventriculography) have been expected to be developed to identify and treat patients at risk for the development of congestive heart failure.
N-terminal pro-brain natriuretic peptide (NTproBNP) has been used for the noninvasive assessment of global LV function.\(^2\) NTproBNP is a 76 amino acid peptide remnant from the cleavage of proBNP to brain natriuretic peptide (BNP).\(^3\) ProBNP is secreted from the cardiac ventricles in response to volume expansion and pressure overload.\(^4,5\) Previous studies have demonstrated that natriuretic peptides levels are correlated with the LV filling pressure in congestive heart failure patients with depressed LV ejection fraction (EF).\(^5,6\) A value of > 1200 pg/ml has a high probability for the diagnosis of heart failure with a negative predictive value of 85%.\(^7\)

Tissue Doppler imaging (TDI) is a new echocardiographic technique employing the Doppler principle to measure the velocity of myocardial segments and other cardiac structures. The ratio between early diastolic transmitial velocity (measured by pulsed Doppler echocardiography) and early mitral annular diastolic velocity (measured by pulsed TDI) has been proposed as the best single Doppler predictor for evaluating LV filling pressure.\(^6,10\) We believe that the analysis of LV long axis function in TDI (peak systolic velocity in TDI of mitral annulus, Sa) provides valuable additive information for the non-invasive assessment of LV global function. This study was designed to evaluate the correlation between the tissue Doppler velocities of mitral annulus and the plasma NTproBNP levels in consecutive patients with DCM, in sinus rhythm, referred for echocardiography. We investigated the value of a novel echocardiographic parameter, E/(Ea×Sa), as a predictor of NTproBNP level in patients with DCM.

**MATERIAL AND METHODS**

**Patients**

We analyzed 58 consecutive patients with DCM, in sinus rhythm, referred for echocardiography. None of the patients presented inadequate echocardiographic images, paced rhythm, mitral prosthesis, severe mitral annular calcification or renal failure (plasma creatinine >250 µmol/l). DCM was diagnosed on the basis of the World Health Organization criteria.\(^11,12\) Briefly, the patients diagnosed with DCM had no significant coronary artery disease (luminal narrowing ≥50%) at coronary angiography, LV end-diastolic diameter (LVEDD) > 112% of predicted LVEDD, and LV shortening fraction < 25%. The predicted LVEDD, corrected for age and body surface area, was calculated by means of the formula of Henry et al (predicted LVEDD = 45.3 x body surface area\(^0.3\) – 0.03 x age – 7.2).\(^13\)

**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 multi-frequency 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.\(^14\) Transmitral flow patterns were recorded from apical four-chamber windows with a 3-5 mm pulsed-sample Doppler volume placed between mitral valve tips. Mitral inflow measurements (at end expiration) included peak early velocity (E), peak late velocity (A), E/A ratio, and E wave deceleration time.\(^15\) 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.\(^15\)

**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 90 to 150 frames per second.\(^16\) A 3-5 mm sample volume was positioned sequentially at the lateral and medial 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 and E/(Ea×Sa) ratios were calculated; the average of the velocities of medial and lateral mitral annulus was used. (Figure 1a-c) All measurements were performed by an experienced echocardiographer blinded to the NTproBNP levels.

**NT-proBNP measurement**

NT-proBNP levels were measured in blood samples.
Figure 1. Bedside measurements of spectral Doppler peak early transmural 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. E/(Ea×Sa) and E/Ea ratios were calculated. The average of the velocities from septal and lateral mitral annulus was used.

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
Statistical analysis used SPSS 11.5 software (SPSS Inc., Chicago, IL, USA) and NCSS 2004 (NCSS, Kaysville, UT, USA). Data are presented as mean value ± standard deviation (SD). Correlation between NTproBNP and several echocardiographic variables was determined by Pearson’s correlation coefficient. The predictive accuracy for NTproBNP levels > 1200 pg/ml was assessed from receiver operating characteristic (ROC) curves. A P value of < 0.05 was accepted as statistically significant.

The study was approved by local institutional review boards. Informed written consent was obtained from all patients.

Table 1. Baseline characteristics of the study group - data is presented as mean ± SD (or percentage).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
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<tbody>
<tr>
<td>Mean age, years</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Female/male gender</td>
<td>19 (32.7%) / 39 (67.3%)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>28.3 ± 4.72</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>98.5 ± 14.2</td>
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<tr>
<td>Toxic cardiomyopathy</td>
<td>26 (44.6%)</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>21 (36.3%)</td>
</tr>
<tr>
<td>Inflammatory cardiomyopathy</td>
<td>8 (13.8%)</td>
</tr>
<tr>
<td>Postpartum cardiomyopathy</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Autoimmune cardiomyopathy</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29 ± 14</td>
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<tr>
<td>E, cm/s</td>
<td>77.2 ± 27.1</td>
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<tr>
<td>Ea, cm/s</td>
<td>61.1 ± 1.16</td>
</tr>
<tr>
<td>Sa, cm/s</td>
<td>5.8 ± 1.7</td>
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<tr>
<td>E/Ea</td>
<td>13.4 ± 5.4</td>
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<tr>
<td>E/(Ea×Sa)</td>
<td>2.52 ± 1.3</td>
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<tr>
<td>PASP, mmHg</td>
<td>42.5 ± 16.7</td>
</tr>
<tr>
<td>NTproBNP, pg/ml</td>
<td>4246 ± 4748</td>
</tr>
<tr>
<td>NTproBNP &gt; 1200 pg/ml</td>
<td>37 (63.8%)</td>
</tr>
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</table>

LV = left ventricle; E = maximal early diastolic transmural velocity; Ea = maximal early mitral annular diastolic velocity; Sa = maximal systolic velocity of mitral annulus; NTproBNP = N-terminal pro-brain natriuretic peptide; PASP = pulmonary artery systolic pressure.

RESULTS
The current study included 58 consecutive patients (mean age: 63 ± 13 years; 39 men) with DCM, in sinus rhythm, referred for echocardiography.
The diagnoses were toxic cardiomyopathy (26 patients), idiopathic cardiomyopathy (21 patients), inflammatory cardiomyopathy (8 patients), postpartum cardiomyopathy (2 patients) and autoimmune cardiomyopathy (1 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.

Simple regression analysis demonstrated a statistically significant linear correlation between \( E/(Ea \times Sa) \) ratio and NTproBNP levels (\( r = 0.73, p < 0.0001 \)). (Fig. 2.a) This was superior to the classical \( E/Ea \) correlation (\( r = 0.49, p < 0.0001 \)). (Fig. 2.b) Significant correlations were also found between NTproBNP levels and pulmonary artery systolic pressure (\( r = 0.53, p < 0.0001 \)), \( Sa \) (\( r = -0.47, p < 0.001 \)), \( Ea \) (\( r = -0.40, p < 0.001 \)), mitral E/A ratio (\( r = 0.34, p < 0.01 \)), E wave (\( r = 0.33, p < 0.001 \)), mitral E deceleration time (\( r = -0.36, p = 0.005 \)). (Fig. 2c) We couldn’t demonstrate significant relationships between NTproBNP and LVEF, left atrial (LA) diameter, LA surface, LA volume, indexed LA volume or end-diastolic LV diameter.

The area under ROC-curve (AUC) for prediction of NTproBNP levels > 1200 pg/ml was greatest for \( E/(Ea \times Sa) \) ratio (AUC = 0.85, \( p < 0.0001 \)), followed by \( E/Ea \) ratio (AUC = 0.80, \( p < 0.0001 \)) and pulmonary artery systolic pressure (AUC = 0.79, \( p < 0.0001 \)). (Fig. 3.a,b) The optimal \( E/(Ea \times Sa) \) cut-off for prediction of NTproBNP levels > 1200 pg/ml was 1.85 (sensitivity of 89%, specificity of 77%). In comparison, an optimal \( E/Ea \) cut-off value of 10.9 had a sensitivity of 84% and a specificity of 71%, respectively a cut-off value of 37 mmHg for pulmonary artery systolic pressure had a sensitivity of 78% and specificity of 71%.

If we calculated the \( E/(Ea \times Sa) \) index at different sites of the mitral annulus (medial, lateral, average), the coefficients of linear correlation (\( r \)) and the areas under ROC-curves (AUC) were: \( r = 0.73, p < 0.0001 \), AUC = 0.85 for average \( E/(Ea \times Sa) \); \( r = 0.70, p < 0.0001 \), AUC = 0.83 for lateral \( E/(Ea \times Sa) \); \( r = 0.65, p < 0.0001 \), AUC = 0.80 for medial \( E/(Ea \times Sa) \), respectively. (Fig. 4) A statistical comparison of the ROC curves demonstrates no significant differences between average \( E/(Ea \times Sa) \) and lateral \( E/(Ea \times Sa) \) (\( p > 0.05 \)), but significant differences between average \( E/(Ea \times Sa) \) and medial \( E/(Ea \times Sa) \) (\( p = 0.02 \), and between lateral \( E/(Ea \times Sa) \) and medial \( E/(Ea \times Sa) \) (\( p = 0.04 \)), respectively. A cut-off of 1.85 had a sensitivity of 93% and specificity of 76% for lateral \( E/(Ea \times Sa) \), and respectively, a sensitivity of 82% and specificity of 74% for medial \( E/(Ea \times Sa) \), to predict a NTproBNP levels > 1200 pg/ml.

**DISCUSSION**

In the present study we analyzed the correlation between a novel tissue Doppler parameter, \( E/(Ea \times Sa) \), and NTproBNP plasma levels in consecutive
patients with DCM, in sinus rhythm, referred for echocardiography. The ratio $E/(Ea \times Sa)$ performed better than other standard echocardiographic and tissue Doppler parameters in predicting high NTproBNP plasma levels.

Although NTproBNP level reflects clinical symptoms and is widely used to manage patients with heart failure, the estimation of NTproBNP is also clinically important.\(^8\)\(^,\)\(^9\)\(^,\)\(^23\) Currently, the American Society of Echocardiography recommends the use of an index of diastolic function ($E/Ea$ ratio) for assessing LV filling pressure.\(^19\) Some authors consider that systolic function is in fact one of the most important determinants of diastolic function.\(^20\) It has been reported that longitudinal function may be a better estimate of LV systolic function compared with EF.\(^21\)\(^,\)\(^22\) The present study demonstrates that combining conventional Doppler echocardiography of the transmitral flow ($E$ velocity) with two TDI parameters ($Ea$ and $Sa$) provides a close prediction of NTproBNP. This novel parameter $E/(Ea \times Sa)$ associates indexes of diastolic function ($E/Ea$) and a parameter that explores LV systolic performance ($Sa$) and therefore may provide supplementary information about the global LV function.\(^8\)\(^,\)\(^9\)\(^,\)\(^23\) NTproBNP is also recognized as a reliable marker of both systolic and diastolic ventricular function.\(^2\)\(^,\)\(^24\) In patients with DCM, the $E/(Ea \times Sa)$ ratio appears to be more accurate than the classical $E/Ea$ index for the estimation of NTproBNP levels in patients in sinus rhythm. The $E/(Ea \times Sa)$ cutoff of 1.85 has a good sensitivity and specificity and can be used in clinical practice to predict with a good accuracy plasma NTproBNP levels superior to 1200 pg/ml.

The combined parameter $E/(Ea \times Sa)$ showed a better correlation with NTproBNP compared to the classic $E/Ea$ and other studied echocardiographic parameters. Ceyhan and Troughton observed significant correlation between $E/Ea$ ratio and BNP levels; results which disagree with another study reporting a weak correlation between $E/Ea$ ratio and NTproBNP.$^{25-27}$ In our study, the average $E/Ea$ ratio showed a moderate correlation with NTproBNP levels ($r = 0.49$, $p < 0.0001$). The best cut-off value for this parameter was 10.9.
The average of velocities determined at multiple sites results in a better prediction of filling pressure.\textsuperscript{28} It has been reported that the average of measurements at the four annular sites gives a better expression of the global LV function.\textsuperscript{23} However, measuring mitral annular velocities from only two corners of the mitral annulus, and using the average of velocities from the medial and lateral site permits an accurate estimation of filling pressures, as recently recommended.\textsuperscript{29} We compared the ROC curves for E/\((Ea \times Sa)\) index at different sites of the mitral annulus (medial, lateral, average); there was no significant differences between the accuracy of average and lateral E/\((Ea \times Sa)\), but the clinical performance for the average and lateral index was superior to medial E/\((Ea \times Sa)\).

Data on the association between echocardiographic (conventional and TDI) parameters and plasma levels of natriuretic peptides are inconsistent.\textsuperscript{23,25,27,30,31} Some studies have found a correlation between natriuretic peptides and Ea, Sa, LVEF, LV end-diastolic diameter, LA diameter, and maximal tricuspid regurgitant flow velocity.\textsuperscript{23,25,27} However, in these studies, no correlation has been demonstrated between natriuretic peptides and other echocardiographic parameters: Ea, mitral E deceleration time, LA surface, E wave, E/A ratio.\textsuperscript{23,25,27,31} We report significant correlations between NTproBNP levels and pulmonary artery systolic pressure, Sa, Ea, E/A ratio, E velocity, and E deceleration time. However, the value of the correlation coefficient was relatively low in our study. We did not find significant relationships between NTproBNP and LVEF fraction, LA diameter, LA surface, LA volume, indexed LA volume or end-diastolic LV diameter. This difference can probably be explained by differences in inclusion criteria: we studied consecutive patients with DCM, in sinus rhythm, while over 60% of heart failure patients in the study by Tretjak et al were in atrial fibrillation.\textsuperscript{27} Mottram et al restricted their analysis to hypertensive patients in sinus rhythm and normal LVEF.\textsuperscript{31}

The E/Ea ratio was superior to other echocardiographic parameters in predicting survival in patients with myocardial infarction.\textsuperscript{32} The value of our novel Doppler parameter 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. 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 (medial 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, paced rhythm, severe mitral calcification, mitral prosthesis or renal failure were not included. Our results must be taken with caution in these subsets of patients.

**CONCLUSIONS**

E/\((Ea \times Sa)\) correlates strongly with plasma NTproBNP level and can be a simple, reproducible and accurate echocardiographic index in patients with DCM in sinus rhythm. There are no significant differences between the accuracy of average and lateral E/\((Ea \times Sa)\), but the clinical performance for the average and lateral index is superior to medial E/\((Ea \times Sa)\). The E/\((Ea \times Sa)\) cut-off of 1.85 has a good sensitivity and specificity and can be used in clinical practice to predict with a good accuracy plasma NTproBNP levels superior to 1200 pg/ml in patients with DCM.

**REFERENCES**


