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TEI INDEX OBTAINED FROM TISSUE DOPPLER IMAGING: CORRELATION WITH NTPROBNP LEVELS IN PATIENTS WITH DILATED CARDIOMIOPATHY

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ABSTRACT. The myocardial performance index (Tei index) determined by the pulsed Doppler is a simple and noninvasive measurement for assessing global left ventricular (LV) function. This index can also be obtained by tissue Doppler imaging (Tei-TDI). The purpose of our study was to assess the relationship between Tei-TDI and N-terminal pro-brain natriuretic peptide (NTproBNP) levels in patients with dilated cardiomyopathy (DCM). Conventional echocardiography and TDI were performed simultaneously with NTproBNP in 50 consecutive patients with DCM, in sinus rhythm. We demonstrated the best linear correlation between Tei-TDI and NTproBNP. The optimal Tei-TDI cut-off for prediction of NTproBNP levels >900 pg/ml was 0.66 (sensitivity of 73% and specificity of 71%). Tei-TDI had a good accuracy to predict high NTproBNP levels and could be used for the global echocardiographic estimation of the LV function in patients with DCM.

Keywords: Natriuretic Peptide, Myocardial Performance Index, Mitral Annulus Velocity, Tissue Doppler Imaging

Abbreviations: BNP = brain natriuretic peptide; E = maximal early diastolic transmitral flow velocity; Ea = maximal early mitral annular diastolic velocity; EDD = end-diastolic diameter; EF = ejection fraction; Tei-TDI = Myocardial performance index assessed by Tissue Doppler Imaging; LA = left atrial; LV = left ventricle; NTproBNP = N-terminal pro-brain natriuretic peptide; Sa = maximal systolic velocity of mitral annulus; TDI = Tissue Doppler Imaging

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 (Thiene G. et al., 2008). 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.

A combined myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time, 'Tei-Index') has been applied in the echocardiographic evaluation of patients with DCM (Tei C. et al., 1995; Tei C. et al., 1997). This index can also be obtained by tissue Doppler imaging (Tei-TDI) (Su H.M. et al., 2006). 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 early diastolic transmitral velocity (measured by pulsed Doppler echocardiography)/early mitral annular diastolic velocity (measured by pulsed TDI) ratio (E/Ea) has been proposed as the best single Doppler predictor for evaluating LV filling pressure (Nagueh S.F. et al., 1997; Ommen S. et al., 2000; Bruch C. et al., 2005). However, this parameter may be inaccurate in some categories of patients (particularly in patients with E/Ea ratio between 8 and 15) (Ommen S. et al., 2000; Wang J. et al, 2007).

N-terminal pro-brain natriuretic peptide (NTproBNP) has been used for the noninvasive assessment of global LV function (Felker G.M. et al., 2006). NTproBNP is a 76 amino acid peptide remnant from the cleavage of proBNP to brain natriuretic peptide (BNP) (Hall C., 2004). ProBNP is secreted from the cardiac ventricles in response to volume expansion and pressure overload (De Lemos J.A. et al., 2003; Maeda K. et al., 1998). 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) (Maeda K. et al., 1998; Kazanegra R. et al., 2001).

This study was designed to evaluate the correlation between Tei-TDI and the plasma NTproBNP levels and to compare with the standard tissue Doppler parameters in consecutive patients with DCM, in sinus rhythm, referred for echocardiography.

MATERIALS AND METHODS

Patients

We analyzed 55 consecutive patients with DCM, in sinus rhythm, referred for echocardiography. No patients were having inadequate echocardiographic

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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 (Richardson P. et al., 1996; Maron B.J. et al., 2006). Briefly, the patients diagnosed as having 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 16 (predicted LVEDD = 45.3 x body surface area 0.3 – 0.03 x age – 7.2).

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 (Lang R.M. et al., 2006). 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 (Quinones M.A. et al., 2002). 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 (Quinones M.A. et al., 2002).

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 (Oki T. et al., 1997) at a frame rate of 90 to 150 frames per second. 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 was calculated (figure 1); the average of the velocities of medial and lateral mitral annulus was used. From TDI recordings, the time interval during diastole (a′) and the duration of the systole Sa-wave (b) were measured. The global myocardial index determined by TDI (GMI-TDI) was calculated as (a - b′)/b′ (figure 2). GMI-TDI was measured at the septal and lateral sites of the mitral annulus, and the average was utilized (Su H.M. et al., 2006). All measurements were performed by two experienced echocardiographers blinded to the NTproBNP levels.

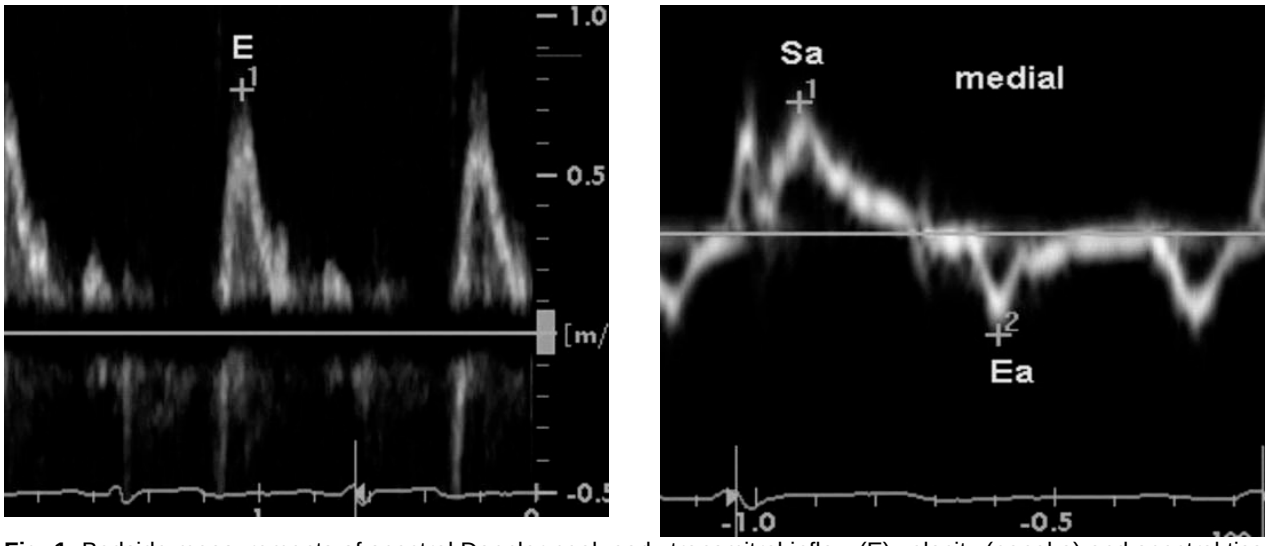


Fig. 1. Bedside measurements of spectral Doppler peak early transmitral inflow (E) velocity (panel a) and spectral tissue Doppler peak early diastolic (Ea) velocities, respectively peak systolic (Sa) velocities, at the medial (panel b) and lateral (panel c) corners of mitral annulus. The average of the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

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 (Barnes S.C. et al., 2004). 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 > 900 pg/ml was assessed from receiver operating characteristic (ROC) curves. A P value of <0.05 was accepted as statistically significant.

RESULTS

The current study included 50 consecutive patients (mean age: 59±11 years; 34 men) with DCM, in sinus rhythm, referred for echocardiography. The diagnoses were toxic cardiomyopathy (23 patients), idiopathic cardiomyopathy (16 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.

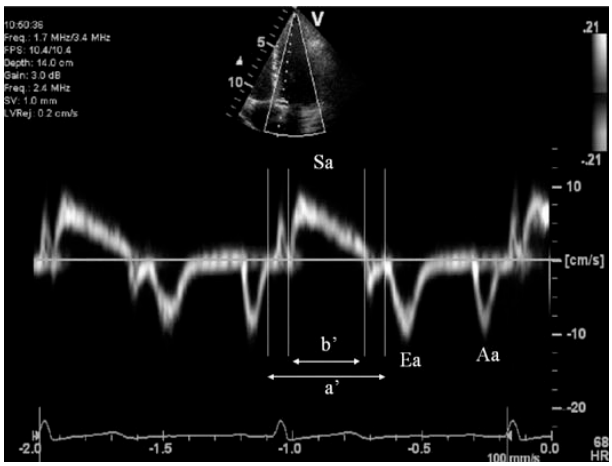


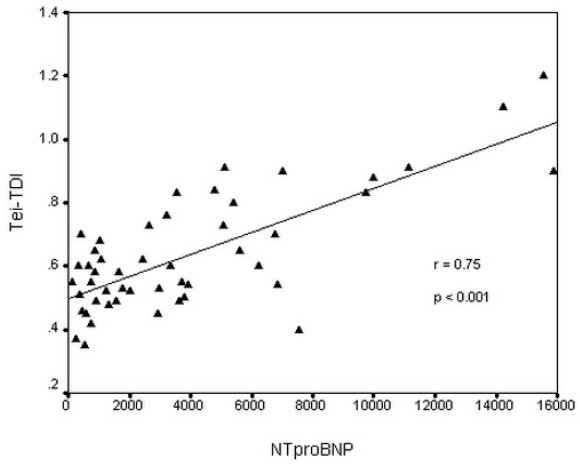
Fig. 2 The myocardial performance index determined by Tissue Doppler Imaging (Tei-TDI) defined as the sum of isovolumetric contraction and relaxation durations divided by ejection time and calculated as (a′ - b′)/b′ ratio (a′ = the time interval during diastole and b′ = the duration of the systole Sa-wave).

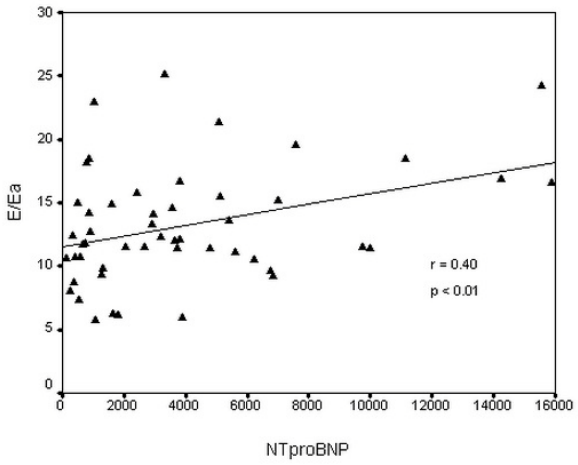
Table 1

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

Characteristics	Data
Mean age, years	59 ± 11
Female/male gender	16 (32%) / 34 (68%)
Body mass index, kg/m^2	29.3 ± 4.51
Heart rate (beats/min)	78 ± 12
Mean arterial pressure, mmHg	96.5 ± 13.9
Toxic cardiomyopathy	23 (46%)
Idiopathic cardiomyopathy	16 (32%)
Inflammatory cardiomyopathy	8 (16%)
Postpartum cardiomyopathy	2 (4%)
Autoimmune cardiomyopathy	1 (2%)
LV ejection fraction (%)	28 ± 15
E, cm/s	86.7 ± 26.1
Ea, cm/s	6.3 ± 1.25
Sa, cm/s	5.6 ± 1.9
E/Ea	13.9 ± 5.3
Tei-TDI	0.62 ± 0.18
PASP, mmHg	46.5 ± 15.8
NTproBNP, pg/ml	3925 ± 3978
NTproBNP > 900 pg/ml	37 (74%)

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.





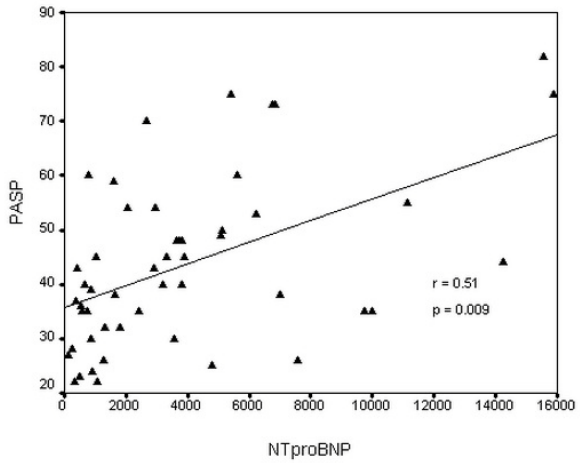


Fig. 3 Scatter plot of the relationship between myocardial performance index determined by Tissue Doppler Imaging (Tei-TDI) (panel a), E/Ea (panel b), pulmonary artery systolic pressure (PASP) (panel c), and N-terminal pro-brain natriuretic peptide (NTproBNP).
E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity; Sa = maximal systolic velocity of mitral annulus.

Simple regression analysis demonstrated a statistically significant linear correlation between Tei-TDI and NTproBNP levels (r=0.75, p<0.001) (figure 3a). This was superior to the classical E/Ea correlation (r=0.40, p<0.01) (figure 3b). Significant correlations were also found between NTproBNP levels and pulmonary artery systolic pressure (r=0.51, p=0.009) (figure 3c), Sa (r= -0.39, p=0.005), Ea (r= -0.30, p=0.02), mitral E/A ratio (r=0.28, p=0.04), mitral E deceleration time (r= -0.26, p=0.04). We couldn't demonstrate significant relationships between NTproBNP and E wave, 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 > 900 pg/ml was greatest for Tei-TDI (AUC=0.73, p<0.001), followed by pulmonary artery systolic pressure (AUC=0.65, p<0.001) and E/Ea ratio (AUC=0.58, p<0.001) (figure 4). The optimal Tei-TDI cut-off for prediction of NTproBNP levels > 900 pg/ml was 0.66 (sensitivity of 73% and specificity of 71%). In comparison, an optimal E/Ea cut-off value of 12.9 had a sensitivity of 64% and a specificity of 61%, respectively a cut-off value of 37.1 mmHg for pulmonary artery systolic pressure had a sensitivity of 70% and specificity of 68%. A statistical comparison of the ROC curves demonstrates significant differences between Tei-TDI and E/Ea ratio (p=0.009), and between Tei-TDI and pulmonary artery systolic pressure (p=0.003), respectively.

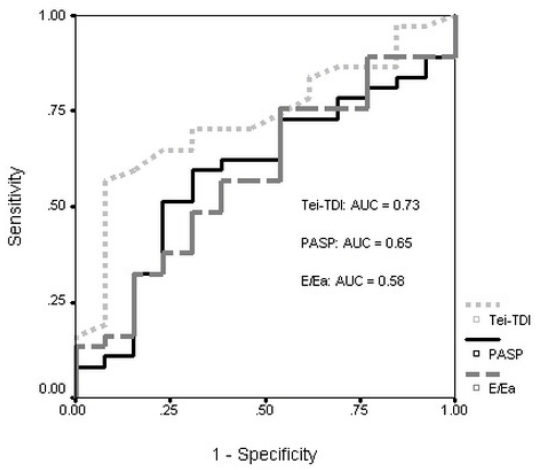


Fig. 4 ROC curves for myocardial performance index determined by Tissue Doppler Imaging (Tei-TDI), pulmonary artery systolic pressure (PASP) and E/Ea in prediction of N-terminal pro-brain natriuretic peptide

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(NTproBNP) levels >900 pg/ml. E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity.

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 (30 patients, 60%). In these patients, NTproBNP was better correlated with Tei-TDI (r=0.65, p=0.001) (figure 5) than with pulmonary artery systolic pressure (r=0.55, p=0.008), E/Ea ratio (r=0.34, p=0.03) or Sa (r= -0.50, p<0.001). The areas under the ROC curves for prediction of NTproBNP levels >900 pg/ml were 0.67 for Tei-TDI (p=0.001) (figure 6), 0.61 for pulmonary artery systolic pressure (p=0.002), 0.52 for E/Ea ratio (p=0.008), and 0.50 for Sa (p=0.01). A statistical comparison of the ROC curves demonstrates significant differences between Tei-TDI and E/Ea, Sa or pulmonary artery systolic pressure (all p<0.05).

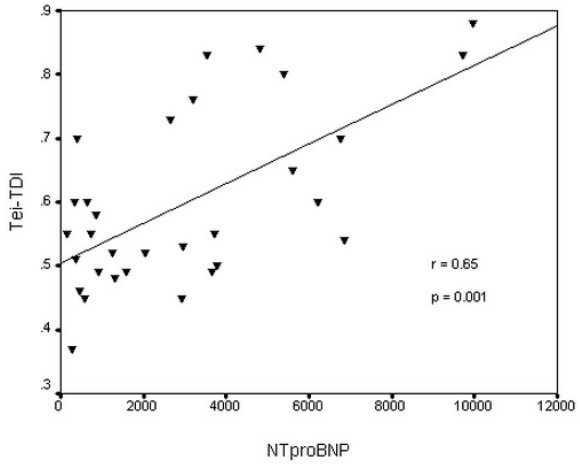

Fig. 5 Scatter plot of the relationship between myocardial performance index determined by Tissue Doppler Imaging (Tei-TDI) and N-terminal pro-brain natriuretic peptide (NTproBNP) in patients with E/Ea between 8 and 15. E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity.

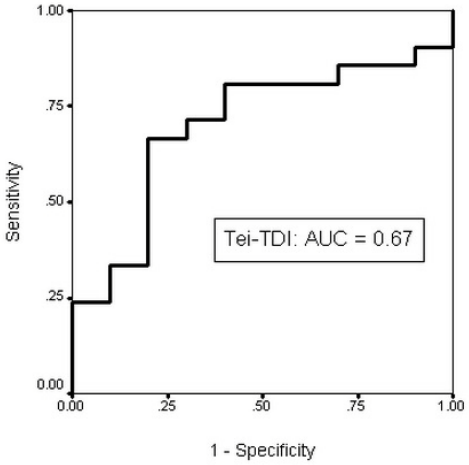

Fig. 6 ROC curves for myocardial performance index determined by Tissue Doppler Imaging (Tei-TDI) in prediction of N-terminal pro-brain natriuretic peptide (NTproBNP) levels >900 pg/ml in patients with E/Ea between 8 and 15. E = maximal early diastolic transmitral velocity; Ea = maximal early mitral annular diastolic velocity.

DISCUSSION

In the present study we analyzed the correlation between different tissue Doppler parameters and NTproBNP plasma levels in consecutive patients with DCM, in sinus rhythm, referred for echocardiography. The Tei-TDI 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 (Hadano Y. et al., 2005). Currently, The American Society of Echocardiography recommends the use of an index of diastolic function (E/Ea ratio) for assessing LV filling pressure (Gottdiener J.S. et al., 2004). Myocardial performances index (Tei index), 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 (Tei C. et al., 1995; Tei C. et al., 1997). This index has been demonstrated to be a powerful and independent prognostic indicator in patients with various cardiac disorders (Dujardin K.S. et al., 1998; Poulsen S.H. et al., 2000; Ascione L. et al., 2003; Arnlov J. et al., 2004). This index can also be obtained also by TDI (Tei-TDI) (Su H.M. et al., 2006). Tei index 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 Tei-TDI increased with worsening of LV diastolic function and can effectively identify the pseudonormal/restrictive mitral inflow pattern (Su H.M. et al., 2006).

The present study demonstrates for the first time that Tei-TDI provides a close prediction of NTproBNP. In our series, the Tei-TDI appears to be more accurate than the classical E/Ea index for the estimation of NTproBNP levels in DCM patients in sinus rhythm. The optimal cut-off value for prediction of NTproBNP levels >900 pg/ml was 0.66 (sensitivity of 73% and specificity of 71%). Tei-TDI index is a marker of LV diastolic and systolic function and reflects LV filling pressure4. Hence, Tei-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 (Felker G.M. et al., 2006; Burke M. et al., 2007).

Ommen S. et al. (2000) and Dokainish H. et al. (2004) suggested that E/Ea between 8 and 15 is unreliable for the prediction of LV function. In our subgroup of patients with E/Ea between 8 and 15, the combined parameter Tei-TDI showed a better correlation with NTproBNP and accuraccy for estimation of high NTproBNP levels compared to the classic E/Ea and other studied echocardiographic parameters.

The relationship between natriuretic peptides and TDI velocities (Ea, Sa, E/Ea) is controversial (Tretjak M. et al., 2005; Mottram P.M. et al., 2003; Arques S. et al., 2007). In a recent study in hypertensive patients by Mottram et al. (2003), no correlation was found between Ea and BNP levels. However, these authors reported a moderate relationship between late diastolic mitral annular velocity and BNP. On the other hand, in a study performed by Tretjak et al. (2005), 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 correlated with NTproBNP. These data are in agreement with our study, where Sa and Ea had a significant but moderate (Sa), respectively low (Ea) correlations with NTproBNP levels. This difference can probably be explained by differences in inclusion criteria: we studied consecutive patients in sinus rhythm, regardless of LV function, 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.

Data on the association between conventional echocardiographic parameters and plasma levels of natriuretic peptides are inconsistent. Some studies have found a correlation between natriuretic peptides and LVEF (Tretjak M. et al., 2005; Elnoamany M.F. et al., 2006), LV end-diastolic diameter (Elnoamany M.F. et al., 2006), left atrial diameter, septal thickness (Ceyhan C. et al., 2008) and maximal tricuspid regurgitant flow velocity (Tretjak M. et al., 2005). However, in these studies, no correlation has been demonstrated between natriuretic peptides and other echocardiographic and Doppler parameters: mitral E deceleration time, left atrial surface, E wave (Tretjak M. et al., 2005), E/A ratio (Ceyhan C. et al., 2008). We report significant correlations between NTproBNP levels and E/A ratio, E velocity, LV ejection fraction 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 LA diameter, LA surface, LA volume, indexed LA volume or EDDLV diameter. We couldn't demonstrate significant relationships between NTproBNP and E wave, LVEF, LA diameter, LA surface, LA volume, indexed LA volume or EDDLV diameter.

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.

CONCLUSIONS

Tei-TDI had a good correlation with plasma NTproBNP levels and can be used for the global echocardiographic estimation of the LV function in patients with DCM, in sinus rhythm. Moreover it proves to be reliable particularly in patients with E/Ea between 8 and 15. The optimal Tei-TDI cut-off of 0.66 has a good sensitivity and specificity and can be used in clinical practice for the estimation of NTproBNP levels > 900 pg/ml.

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