

## Original Research

# The Relationship Between the Time Interval Difference of Isovolumic Relaxation ( $T_{IVRT-IVRTa}$ ) and Serum Levels of N-Terminal Pro-Brain Natriuretic Peptide in Patients with Intermediate E/Ea Ratio

IOANNA ZACHAROPOULOU<sup>1,2</sup>, CRISTIAN MORNOȘ<sup>2</sup>, ATHANASIOS J. MANOLIS<sup>1</sup>, NIKOS KOUREMENOS<sup>1</sup>, ATHANASIOS TSOUKAS<sup>1</sup>, ANDREAS PITTARAS<sup>1</sup>, LEONIDAS POULIMENOS<sup>1</sup>, ȘTEFAN-IOȘIF DRĂGULESCU<sup>2</sup>

<sup>1</sup>Department of Cardiology, Asklepieion General Hospital, Athens, Greece; <sup>2</sup>“Victor Babeș” University of Medicine and Pharmacy, Timișoara, Romania

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Address:  
 Ioanna Zacharopoulou

Dept. of Cardiology  
 Asklepieion General  
 Hospital  
 1 Vas Pavlou St.  
 166 73 Voula  
 Athens, Greece  
 e-mail:  
[joanzachar@yahoo.gr](mailto:joanzachar@yahoo.gr)

**Introduction:** The ratio of early diastolic transmitral velocity to early mitral annular diastolic velocity (E/Ea) can be used to group patients according to filling pressures. However this relationship has not been validated in the intermediate group (E/Ea=8-15). The time difference between the onset of E and Ea also correlates with left ventricular (LV) filling pressures. The purpose of our study was to evaluate the correlation between the time interval difference of isovolumic relaxation ( $T_{IVRT-IVRTa}$ ) and N-terminal pro-brain natriuretic peptide (NTpro-BNP) in patients with an intermediate E/Ea ratio.

**Methods:** Echocardiography was performed simultaneously with NTpro-BNP measurement in 60 consecutive patients who had an intermediate E/Ea and were in sinus rhythm. Ea and the isovolumic relaxation time (IVRTa) at the septal and lateral sites of the mitral annulus were measured using pulsed tissue Doppler and the average was utilised. Pulsed Doppler was used to measure E and IVRT. E/Ea and IVRT-IVRTa ( $T_{IVRT-IVRTa}$ ) were calculated.

**Results:** We demonstrated significant correlations between  $T_{IVRT-IVRTa}$  and NTpro-BNP ( $r=-0.72$ ,  $p<0.001$ ), maximal systolic velocity of the mitral annulus (Sa:  $r=-0.50$ ,  $p<0.001$ ), pulmonary artery systolic pressure ( $r=0.42$ ,  $p=0.002$ ), IVRTa ( $r=-0.27$ ,  $p=0.03$ ), LV ejection fraction (LVEF:  $r=-0.26$ ,  $p=0.04$ ), IVRT ( $r=-0.24$ ,  $p=0.04$ ). We were unable to demonstrate significant relationships between NTpro-BNP and E deceleration time, left atrial diameter/area/volume, Ea or E. By a multiple linear regression analysis, including  $T_{IVRT-IVRTa}$ , IVRT, IVRTa, E/Ea, LVEF, pulmonary artery systolic pressure and Sa as potential determinants,  $T_{IVRT-IVRTa}$  ( $\beta=-0.57$ ,  $p<0.001$ ) was shown to be the best independent predictor of NTpro-BNP ( $r^2=0.68$ ,  $p<0.001$ ).

**Conclusions:**  $T_{IVRT-IVRTa}$  correlates strongly with NTpro-BNP levels in patients with intermediate E/Ea, and could be used as a simple echocardiographic index, with reasonable accuracy.

**T**issue Doppler imaging (TDI) is a novel echocardiographic technique that permits the measurement of mitral annular and myocardial velocities.<sup>1</sup> The ratio between early diastolic transmitral velocity (E, measured by pulsed Doppler echocardiography) and

early mitral annular diastolic velocity (Ea, measured by pulsed tissue Doppler) has been demonstrated to correlate with left ventricular (LV) filling pressure.<sup>1,2</sup> This parameter may be inaccurate in some categories of patients, particularly in patients with an intermediate E/Ea ratio (between

8 and 15) and patients with regional LV dysfunction.<sup>3</sup> The difference between the intervals from the R on the electrocardiogram to the onset of early diastolic velocity ( $T_E$ ) and to the onset of mitral inflow ( $T_{Ea}$ ), expressed as  $T_{E-Ea}$ , has also been shown to be useful for predicting LV filling pressures and for determining impaired diastolic function.<sup>4</sup>  $T_{E-Ea}$  is dependent on LV relaxation and left atrial (LA) pressure. The onset of Ea is delayed when LV relaxation is impaired, resulting in a prolonged myocardial isovolumic relaxation time (IVRTa), while there is a shortening of blood-flow derived isovolumic relaxation time (IVRT), which is explained by the increased driving force of elevated LA pressure. The relative time difference between IVRT and IVRTa can easily be calculated ( $T_{IVRT-IVRTa}$ ), as both IVRT and IVRTa are commonly measured in clinical practice, unlike the time difference between R and the onset of E or Ea.<sup>5</sup>

N-terminal pro-brain natriuretic peptide (NTpro-BNP) has been used for the non-invasive assessment of LV function.<sup>6</sup> NTpro-BNP is a 76-amino-acid peptide (biologically inactive) remnant from the cleavage of pro-BNP to brain natriuretic peptide (biologically active).<sup>7</sup> Pro-BNP is secreted from the cardiac ventricles in response to volume expansion and pressure overload.<sup>8,9</sup> Previous studies have demonstrated that natriuretic peptide levels are correlated with the LV filling pressure in congestive heart failure patients who have a depressed LV ejection fraction (LVEF).<sup>9,10</sup>

This study was designed to evaluate the correlation between the time interval difference of isovolumic relaxation ( $T_{IVRT-IVRTa}$ ) and plasma NTpro-BNP levels in consecutive patients with an intermediate E/Ea ratio (between 8 and 15) in sinus rhythm, referred for echocardiography.

## Methods

### Study population

We screened 137 consecutive patients with LV dysfunction (according to the recommendations of the European Association of Echocardiography/American Society of Echocardiography<sup>11</sup>) who were referred for echocardiography and were in sinus rhythm. Patients with an inadequate echocardiographic image, congenital heart disease, paced rhythm, severe mitral valvular disease, mitral prosthesis, pericardial disease, acute coronary syndrome, coronary artery bypass with-

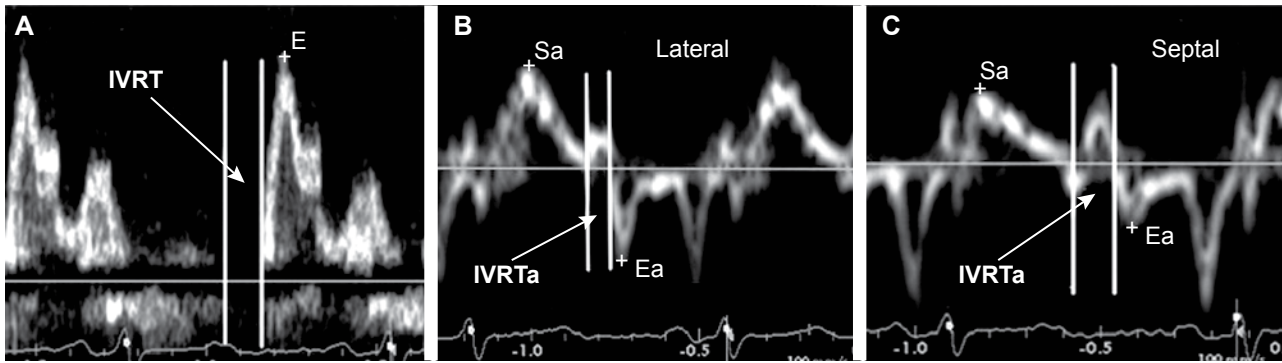
in 72 hours, or renal failure were excluded. Only 60 patients with an intermediate E/Ea ratio (between 8 and 15) formed our study group. All patients gave their informed consent.

### Echocardiographic examination

Conventional echocardiography and TDI were performed simultaneously with determination of NTpro-BNP. Two-dimensional and Doppler echocardiographic examinations were performed with an ultrasonographic system (Vivid 7 General Electric, Milwaukee WI, USA) 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.<sup>12</sup> 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 (Figure 1a). Care was taken to obtain the smallest possible angle between the direction of transmitral 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.<sup>13</sup> IVRT was measured as the time difference between aortic valve closure (from sub-aortic valve pulsed Doppler flow) to the onset of E from transmitral flow. 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.<sup>13</sup>

### Tissue Doppler measurements

The tissue Doppler program was set in pulsed-wave Doppler mode. The motion of the mitral annulus was recorded in the apical four-chamber view at a frame rate of 80 to 140 frames per second. A 3-5 mm sample volume was positioned sequentially at the lateral (Figure 1b) and septal (Figure 1c) 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:<sup>14</sup> one during the early phase of diastole (Ea), and another during the late phase of diastole (Aa). A major positive sys-



**Figure 1.** Transmitral (A) and tissue Doppler velocities. The average of the velocities from the lateral (B) and septal (C) sites of the mitral annulus was used to calculate the E/Ea ratio and  $T_{IVRT-IVRTa}$ . A – atrial diastolic flow from transmitral flow; E – maximal early diastolic transmitral velocity; Ea – maximal early mitral annular diastolic velocity; IVRT – isovolumic relaxation time from transmitral flow; IVRTa – myocardial isovolumic relaxation time; Sa – maximal mitral annular systolic velocity.

tolic velocity was recorded with the movement of the annulus toward the cardiac apex during systole. The peak myocardial systolic velocity (Sa) was defined as the maximum velocity during systole, excluding the isovolumic contraction. All velocities were recorded for five consecutive cardiac cycles at end expiration, and results were averaged. All tissue Doppler signals were recorded at a horizontal time sweep of 100 mm/s. The E/Ea ratio was calculated; the average of the velocities of the septal and lateral mitral annulus was used. The myocardial isovolumic relaxation time (IVRTa) was measured from end of systolic myocardial velocity during ejection (Sa) to onset of the early diastolic myocardial velocity (Ea). This was done at the left lateral and septal corner of the mitral annulus and the average of the times was used; the time difference IVRT-IVRTa was further calculated to obtain the  $T_{IVRT-IVRTa}$  parameter. All measurements were performed by two experienced echocardiographers blinded to the NTpro-BNP levels.

### NTpro-BNP measurement

NTpro-BNP 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.<sup>15</sup> 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. We used a cut-off of 900 pg/ml for NTpro-BNP, as recommended in the PRIDE study (NTpro-BNP Investigation of Dyspnea in the Emergency Department).<sup>16</sup>

### Statistical analysis

Data are presented as mean value  $\pm$  standard deviation (SD). Pearson's correlation was used to investigate relations between variables. We performed multivariate logistic regression analysis to assess the influence on NTpro-BNP of variables reaching statistical significance on univariate analysis ( $p < 0.05$ ). 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, IL, USA).

### Results

The current study included 60 consecutive patients (mean age:  $61 \pm 13$  years; 32 women) with an intermediate E/Ea ratio, in sinus rhythm, referred for echocardiography. The admitting diagnoses were coronary artery disease (31 patients), non-ischaemic cardiomyopathy (19 patients), systemic hypertension (8 patients), valvular disease (aortic regurgitation: 2 patients). The 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  $T_{IVRT-IVRTa}$  and NTpro-BNP levels ( $r = -0.72$ ,  $p < 0.001$ ) (Figure 2a). This was superior to the classical E/Ea correlation ( $r = 0.30$ ,  $p = 0.03$ ) (Figure 2b). Significant correlations were also found between NTpro-BNP levels and Sa ( $r = -0.50$ ,  $p < 0.001$ ) (Figure 2c), pulmonary artery systolic pressure ( $r = 0.42$ ,  $p = 0.002$ ) (Figure 2d),

**Table 1.** Baseline characteristics of the study group. Data are presented as mean  $\pm$  SD or n (%).

Mean age, years	61 $\pm$ 13
Female/male	32 (53.3) / 28 (47.7)
Body mass index, kg/m <sup>2</sup>	28 $\pm$ 5.6
Heart rate, beats/minute	76 $\pm$ 13
Mean arterial pressure, mmHg	97 $\pm$ 14.2
Coronary artery disease	31 (51.7)
Non-ischaemic cardiomyopathy	19 (31.7)
Systemic hypertension	8 (13.3)
Valvular dysfunction	2 (3.3)
Left ventricular ejection fraction	40 $\pm$ 13
E, cm/s	79 $\pm$ 24
Ea, cm/s	7.1 $\pm$ 2.1
Sa, cm/s	6.4 $\pm$ 2.3
E/Ea ratio	11.2 $\pm$ 1.8
T <sub>IVRT-IVRTa</sub> , ms	-27 $\pm$ 45
Pulmonary artery systolic pressure, mmHg	41 $\pm$ 14
NTpro-BNP, pg/ml	2603 $\pm$ 2597
NTpro-BNP >900 pg/ml	38 (63.3)

E – maximal early diastolic transmitral velocity; Ea – maximal early mitral annular diastolic velocity using the average of the medial and lateral sites of mitral annulus; IVRT – isovolumic relaxation time; NTpro-BNP – N-terminal pro-brain natriuretic peptide; Sa – maximal systolic velocity of mitral annulus.

mitral E/A ratio ( $r=0.32$ ,  $p=0.01$ ), IVRTa ( $r=-0.27$ ,  $p=0.03$ ), LVEF ( $r=-0.26$ ,  $p=0.04$ ) and IVRT ( $r=-0.24$ ,  $p=0.04$ ). We were unable to demonstrate significant relationships between NTpro-BNP and mitral E deceleration time, left atrial diameter, Ea, E wave, left atrial area, left atrial volume, indexed left atrial volume, or LV end-diastolic volume.

The areas under the ROC curves for prediction of NTpro-BNP levels >900 pg/ml were 0.80 for T<sub>IVRT-IVRTa</sub> ( $p=0.001$ ) (Figure 3a), 0.74 for pulmonary artery systolic pressure ( $p=0.002$ ) (Figure 3b), 0.70 for E/Ea ratio ( $p=0.008$ ) (Figure 3c), and 0.67 for Sa ( $p=0.02$ ). A statistical comparison of the ROC curves demonstrated significant differences between T<sub>IVRT-IVRTa</sub> and E/Ea ( $p=0.003$ ), and between T<sub>IVRT-IVRTa</sub> and pulmonary artery systolic pressure ( $p=0.008$ ). The optimal cut-off value for T<sub>IVRT-IVRTa</sub>, -25.5 ms, had a sensitivity of 82% and a specificity of 70% for predicting NTpro-BNP levels >900 pg/ml. The sensitivity and specificity for detecting an elevated NTpro-BNP level (>900 pg/ml) using a cut off-value of T<sub>IVRT-IVRTa</sub> being  $\leq 0$  were 60% and 77%, respectively.

By multiple linear regression analysis (Table 2), including T<sub>IVRT-IVRTa</sub>, IVRT, IVRTa, E/Ea ratio, LVEF, pulmonary artery systolic pressure, mitral E/A ratio and Sa wave as potential determinants, T<sub>IVRT-</sub>

IVRTa ( $\beta=-0.57$ ,  $p<0.001$ ) was shown to be the best independent predictor of NTpro-BNP level (cumulative  $r^2=0.68$ ,  $r=0.79$ ,  $p<0.001$ ).

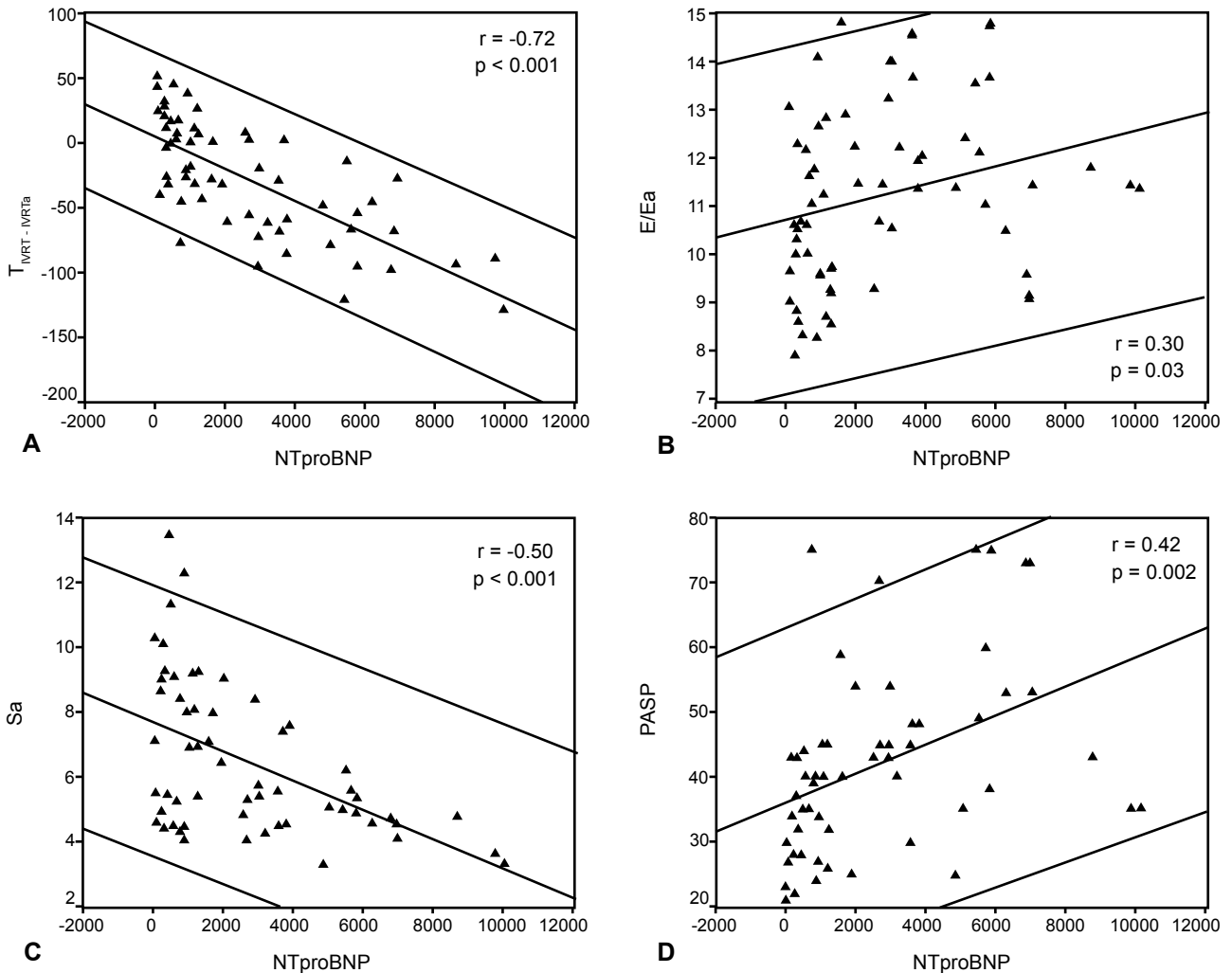
T<sub>IVRT-IVRTa</sub> showed a better correlation with NTpro-BNP in patients with normal LV ejection fraction (EF  $\geq 50\%$ ) (17 patients, 28.3%,  $r=0.78$ ,  $p<0.001$ ) compared with those with depressed LVEF (<50%) (43 patients, 71.7%,  $r=0.67$ ,  $p<0.001$ ). The area under the ROC curve for prediction of NTpro-BNP levels >900 pg/ml was 0.87 ( $p<0.001$ ) in patients with normal LVEF and 0.71 ( $p<0.001$ ) in those with reduced LVEF.

## Discussion

In the present study we demonstrated that the difference between the blood-flow derived isovolumic relaxation time and the myocardial isovolumic relaxation time, measured as T<sub>IVRT-IVRTa</sub>, is strongly correlated with NTpro-BNP plasma levels in consecutive patients with an E/Ea ratio between 8 and 15, in sinus rhythm. By multiple linear regression analysis T<sub>IVRT-IVRTa</sub> was shown to be the best independent predictor of NTpro-BNP level.

The relationship between natriuretic peptides and tissue Doppler parameters (Ea, Sa, E/Ea) is controversial.<sup>17-19</sup> Currently, the American Society of Echocardiography recommends the use of the E/Ea ratio for assessing LV filling pressure,<sup>20</sup> but Ommen et al<sup>2</sup> and Dokainish et al<sup>21</sup> suggested that an intermediate E/Ea (between 8 and 15) is a grey zone for the prediction of LV filling pressures. In patients with regional wall motion abnormalities, the difference between the velocities of different mitral annular sites is generally exaggerated.<sup>1,2,22</sup> It has been reported that the average of measurements at the four annular sites gives a better expression of the global LV function.<sup>23</sup> However, measuring mitral annular parameters from only two corners of the mitral annulus, and using the average from the septal and lateral site permits an accurate estimation of filling pressures, as recently recommended.<sup>24</sup> In our study we used tissue Doppler measurements at only two sites (medial and lateral mitral annulus).

Previous studies have shown a correlation between natriuretic peptides and septal thickness,<sup>25</sup> LV end-diastolic diameter,<sup>23</sup> LVEF,<sup>17,23</sup> left atrial diameter,<sup>25</sup> maximal tricuspid regurgitant flow velocity,<sup>17</sup> Ea,<sup>17,26</sup> and Sa.<sup>17</sup> In these studies no correlation was demonstrated between natriuretic peptides and other echocardiographic and Doppler parameters: E/A



**Figure 2.** Scatter plot of the relationship between  $T_{IVRT-IVRTa}$  (A), E/Ea ratio (B), Sa (C), pulmonary artery systolic pressure (PASP) (D), and N-terminal pro-brain natriuretic peptide (NTpro-BNP) in the overall population. The average of the velocities from the lateral and septal sites of the mitral annulus was used to calculate relevant parameters. E – maximal early diastolic transmitral velocity; Ea – maximal early mitral annular diastolic velocity; IVRTa – myocardial isovolumic relaxation; IVRT – isovolumic relaxation time from transmitral flow; Sa – maximal mitral annular systolic velocity.

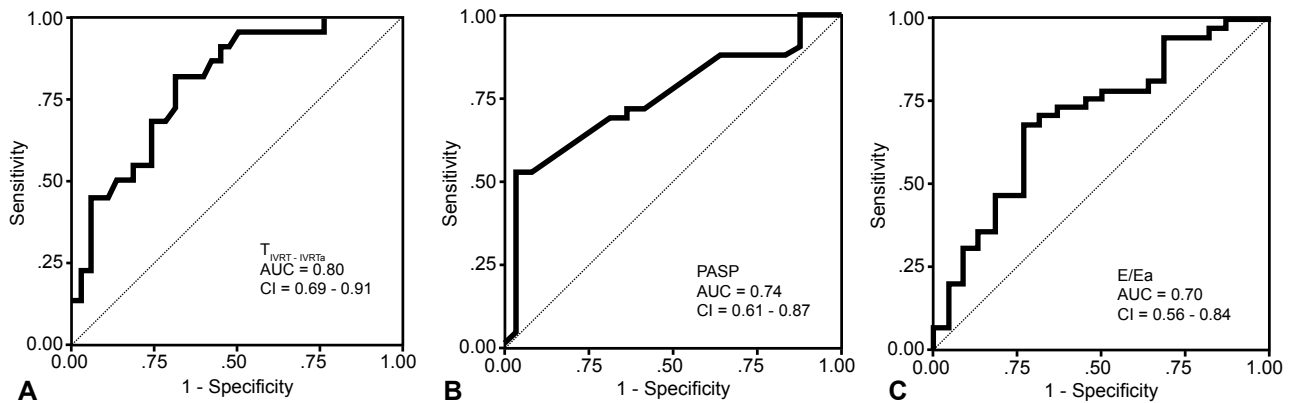
ratio,<sup>25</sup> mitral E deceleration time,<sup>17</sup> E wave<sup>17</sup> or left atrial area.<sup>17</sup> Ceyhan<sup>25</sup> and Troughton<sup>26</sup> observed significant relationships between BNP levels and E/Ea ratio, results that disagree with another study reporting a weak correlation between E/Ea ratio and NTpro-BNP levels.<sup>17</sup>

In the present study, we report significant correlations, though with a relatively low correlation coefficient, between NTpro-BNP levels and E/Ea ratio, Sa, pulmonary artery systolic pressure, mitral E/A ratio, IVRTa, LVEF and IVRT. We did not find significant relationships between NTpro-BNP and mitral

**Table 2.** Results of multivariate analysis in the overall population.

Determinant of NTpro-BNP	$\beta$ coefficient	p
$T_{IVRT-IVRTa}$	-0.57	<0.001
$T_{IVRT}$	0.69	0.33
$T_{IVRTa}$	0.78	0.29
E/A ratio	-0.20	0.12
E/Ea ratio	0.33	0.39
Left ventricular ejection fraction	0.05	0.66
Pulmonary artery systolic pressure	0.08	0.46
Sa wave	-0.28	0.03

A – maximal late diastolic transmitral velocity. Other abbreviations as in Table 1.



**Figure 3.** Receiver operating characteristic (ROC) curves for  $T_{IVRT-IVRTa}$  (A), pulmonary artery systolic pressure (PASP) (B) and E/Ea ratio (C) in the prediction of N-terminal pro-brain natriuretic peptide levels  $>900$  pg/ml in the overall population. The average of the velocities from the lateral and septal sites of the mitral annulus was used to calculate relevant parameters. AUC – area under curve; CI – confidence interval; E – maximal early diastolic transmitral velocity; Ea – maximal early mitral annular diastolic velocity; IVRTa – myocardial isovolumic relaxation time; IVRT – isovolumic relaxation time from transmitral flow; LV – left ventricle.

E deceleration time, left atrial diameter, Ea, E wave, left atrial area, left atrial volume, indexed left atrial volume or end-diastolic LV volume. This difference can probably be explained by differences in inclusion criteria: we studied consecutive patients with an intermediate E/Ea ratio, in sinus rhythm, whereas over 60% of the heart failure patients in the study by Tretjak et al<sup>17</sup> were in atrial fibrillation, while Mottram et al<sup>18</sup> restricted their analysis to hypertensive patients who were in sinus rhythm and had a normal LVEF.

In normal subjects, the LV isovolumic relaxation phase is short and the diastolic suction results in an onset of mitral E that is simultaneous with or slightly after the Ea.<sup>27</sup> With normal ageing IVRT increases, with regard to both blood flow and myocardial motion. However, IVRT from blood flow has been found to be 20-30 ms longer than IVRTa throughout the age range of 20-81 years in healthy subjects.<sup>28</sup> When atrial contraction is not sufficient to maintain adequate stroke volume, left atrial pressure rises and the relations between E and Ea, and IVRT and IVRTa disappear;<sup>27</sup> Ea falls and the onset of Ea is delayed, concomitantly with an increase in E velocity and a shortening of IVRT.<sup>5</sup> Deterioration of active relaxation results in a prolongation of IVRT; however, when left ventricular filling pressure elevates, the mitral valve opens earlier and IVRT shortens. This shortening is not seen when IVRT is measured with tissue Doppler imaging (IVRTa). Then, IVRTa is prolonged, with the deceleration of active relaxation being independent of left ventricular filling pressure.<sup>29</sup>

The present study demonstrates for the first time that  $T_{IVRT-IVRTa}$  provides a close prediction of NTpro-BNP in consecutive patients with an E/Ea ratio between 8 and 15, in sinus rhythm. In our series, the  $T_{IVRT-IVRTa}$  index appears to be more accurate than the classical E/Ea index for the estimation of NTpro-BNP levels. The optimal cut-off value for prediction of NTpro-BNP levels  $>900$  pg/ml was -25.5 ms. In our study,  $T_{IVRT-IVRTa}$  correlated well with levels of NTpro-BNP, regardless of LVEF.

Our results should be considered in the context of several 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 manoeuvre, as these Doppler parameters are difficult to record and are thus not suitable for simple screening. We limited the tissue Doppler measurements to two sites (septal and lateral mitral annulus) and we did not examine anterior and posterior velocities, which 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 viewed with caution in these subsets of patients.

## Conclusions

T<sub>IVRT-IVRTa</sub> correlates strongly with plasma NTpro-BNP levels in patients with an E/E<sub>a</sub> ratio between 8 and 15, in sinus rhythm, and could be used as a simple echocardiographic index, with reasonable accuracy, regardless of LV ejection fraction.

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