Serum NT-proBNP Concentrations in the Early Phase Do Not Predict the Severity of Systolic or Diastolic Left Ventricular Dysfunction Among Patients With ST-Elevation Acute Myocardial Infarction

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The cohort included 55 consecutive patients with first ST elevation acute myocardial infarction (STEAMI) who underwent reperfusion. Blood samples were drawn for N-terminal pro B-type natriuretic peptide (NT-proBNP), highly-sensitive C-reactive protein (hs-CRP), creatinine kinase (CK), cardiac troponin I (cTnI), and white blood cell (WBC) count within 24 hours of admission. Transthoracic echocardiography, performed within the same time frame, assessed left ventricular (LV) systolic function, as well as diastolic function. Variables significantly associated with poor systolic LV dysfunction were hs-CRP, peak CK, cTnI, and WBC. There was no significant correlation between NT-proBNP and systolic function early after STEAMI ($p = 0.49$). Among patients with diastolic dysfunction, there was no significant correlation between NT-proBNP levels and peak mitral E-wave velocity to peak initial A-wave velocity (E/A ratio) ($r = 0.19$, $p = 0.18$) or E-wave deceleration time ($r = 0.22$, $p = 0.15$). Thus, NT-proBNP levels in the early phase after STEAMI were not indicative of systolic or diastolic function.

Introduction

B-type natriuretic peptide (BNP) is a hormone secreted from cardiac ventricular myocytes in response to increased pressure and volume.[1] BNP is produced by cleavage of a precursor protein (proBNP) to BNP and the biologically inactive peptide N-terminal (NT)-proBNP. NT-proBNP is more stable in circulating blood and has a longer half-life, and potentially could be more useful for risk prediction.[2,3] BNP causes natriuresis, diuresis, vasodilatation, and inhibition of the sympathetic nervous system, the renin-angiotensin–aldosterone axis, and myocyte growth.[4-6] Plasma

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concentrations of BNP are influenced by a number of factors, including age, female gender, renal failure, and various medications.[7,8] In patients with chronic heart failure, BNP is useful for diagnosis, follow-up, and prediction of outcome.[9-11] In acute coronary syndromes (ACS), BNP levels are elevated, and predict short- and long-term mortality, independent of left ventricular (LV) function.[12-15] The correlation between BNP levels and systolic LV function after ST elevation acute myocardial infarction (STEAMI) is controversial, and depend on the timing of BNP examination.[16-23] In patients shortly after STEAMI, the relationship between diastolic function and BNP levels has not been widely described. Therefore, the aim of our study was to assess the correlation between serum NT-proBNP levels in the early postinfarction period after STEAMI with the systolic and diastolic LV function.

Methods

We prospectively followed up 55 consecutive patients with a first STEAMI treated with primary percutaneous intervention (PCI) or thrombolysis within 6 hours of symptom onset. Exclusion criteria included age <18 years, previous AMI, cardiogenic shock, renal failure (creatinine >1.5 mg/dL), prior LV dysfunction, and unsuccessful PCI (defined as residual diameter stenosis of culprit artery >20% and TIMI flow <3) or unsuccessful thrombolysis (defined as resolution of the ST-segment elevation by <50%). Written informed consent was obtained from all patients before enrollment. All patients were evaluated for baseline demographic and clinical characteristics, as well as treatment modalities before and during the hospital course.

Blood samples were drawn for serum NT-proBNP, highly-sensitive C-reactive protein (hs-CRP), cardiac troponin I levels (cTnI), and white blood cell (WBC) count within 24 hours after admission. Creatine kinase (CK) levels were determined on admission and every 8 hours thereafter for the first 48 hours. Maximum CK activity was defined as the highest value obtained.

NT-proBNP was assayed by an electrochemiluminescence immunoassay "ECLIA," on Roche Elecsys 2010 analyzer. hs-CRP was assayed using the Roche/Integra 800 Analyzer by a particle-enhanced immunoturbidimetric method, using latex particles coated with monoclonal anti-CRP antibodies. The day-to-day variation (expressed as CV%) was 3.5% at 0.43 mg/dL, 2.9% at 2.0 mg/dL, and 1.7% at 5.0 mg/dL. Troponin I analysis was performed using the DPC's IMMULITE turbo kit. Based on the 98th percentile, the recommended cutoff value was 1.0 ng/mL. The within-run precision at this level was 3.3%. The detection limit was 0.5 ng/mL, with a within-run precision of 8.8%. The day-to-day variation (expressed as CV%) was 13.7% at 0.7 ng/mL and 6.2% at 12.5 ng/mL.

In all patients, LV systolic and diastolic function were assessed within 24 hours after admission by transthoracic two-dimensional echocardiography. Systolic LV function was assessed by qualitative scoring of ejection fraction (EF), as well as by the regional wall motion score index (RWMSI). Normal function was considered as an estimated LV EF of >50%, mild impairment as LV EF 40–50%, moderate as LV EF 30–39%, and severe as LV EF <30%. Wall motion was also calculated based on a 16-segment model with segments graded as being normokinetic, hypokinetic, akinetic, or dyskinetic and respectively scored on a scale ranging from 1 to 4.[24] The total wall motion score was divided by 16 to derive the RWMSI. The presence of diastolic dysfunction was determined based on the pulse-Doppler transmitral flow velocity curve, measuring the ratio of peak mitral E-wave velocity to peak mitral A-wave velocity (E/A ratio) and the deceleration time (DT) of the mitral E-wave velocity. Diastolic dysfunction was classified in 3 categories of increasing severity[25]: (1) Impaired relaxation, defined as DT >240 msec with E/A ratio <1; (2) pseudo-normal, defined as DT = 160–200 msec with E/A ratio = 1–1.5; (3) restrictive pattern, defined as DT <160 msec with E/A ratio >2.

Statistical Analysis

Statistical analyses were done using SPSS statistical software version 11. Continuous variables are expressed as mean ± standard deviation. Differences between continuous variables were assessed by Student's t test. Categories were compared by using the χ^2-test. Significance level was set at p value <5%. Bivariate correlations were assessed by using the bivariate correlation test. To evaluate the independent relation between NT-proBNP and LV systolic and diastolic function,

covariates that were significantly associated with NT-proBNP and systolic or diastolic function were evaluated in a multivariable logistic regression. Receiver operating curve (ROC) analysis was used to determine the best predictor of LV function among several predictive parameters.

Results

Our cohort included 55 consecutive patients with a first STEAMI, in whom reperfusion therapy was achieved by primary PCI in 40 (73%) patients and thrombolysis in 15 (27%) patients. Their mean age was 59 (±11.7) years, and 40 (73%) were men. Thirty-six percent of the patients had anterior wall STEAMI. There were 19 (34.5%) patients with normal LV function, 17 (31%) with mild LV dysfunction, and 19 (34.5%) with moderate or severe LV dysfunction. The baseline characteristics and clinical findings of our cohort are presented in Table I, based on systolic function.

NT-proBNP and Systolic Dysfunction

Variables significantly associated with poor systolic LV function were hs-CRP levels ($p < 0.01$), peak CK levels ($p < 0.01$), peak cTnI levels ($p = 0.05$), and WBC count ($p = 0.04$). Similar results were obtained when we used the RWMSI as a continuous variable: peak CK ($p < 0.01$, $r = 0.51$) (Figure 1A); cTnI ($p < 0.01$, $r = 0.43$) (Figure 1B); hs-CRP ($p < 0.01$, $r = 0.37$) (Figure 1C); and WBC ($p = 0.04$, $r = 0.28$) (Figure 1D). There was no significant correlation between RWMSI and NT-proBNP levels ($p = 0.49$, $r = 0.1$) (Figure 1E). On

Table I. Baseline characteristics of the cohort based on severity of LV dysfunction.

	Normal LV Function	Mild LV Dysfunction	Moderate–Severe LV Dysfunction
Age, yr	56 (9)	59 (12)	62 (13)
Female sex, %	26	12	42
Diabetes mellitus, %	26	12	21
Hypertension, %	32	41	53
Hyperlipidemia, %	63	65	79
Smoking, %	42	59	42
Anterior MI, %	5	24	79*
Killip >2, %	11	0	16*
WBC, $\times 10^3$/mL	11.4 (3.4)	11.5 (2.6)	13.6 (4)*
Peak CK, U/L	1,071 (921)	1,848 (1,339)	2,981 (1,296)*
CTnI, ng/mL	68 (64)	50 (65)	79 (41)*
hs-CRP, mg/dL	3 (2.7)	4.7 (4)	5.8 (3.5)*
NT-proBNP, pg/mL	2,123 (1,539)	1,998 (1,524)	2,733 (2,595)

*$p < 0.05$.

Continuous variable presented as x ± SD.

BNP = B-type natriuretic peptide, CK = creatinine kinase, CRP = C-reactive protein, CTnI = cardiac troponin I, hs = highly-sensitive, MI = myocardial infarction, NT = N-terminal, WBC = white blood cells.

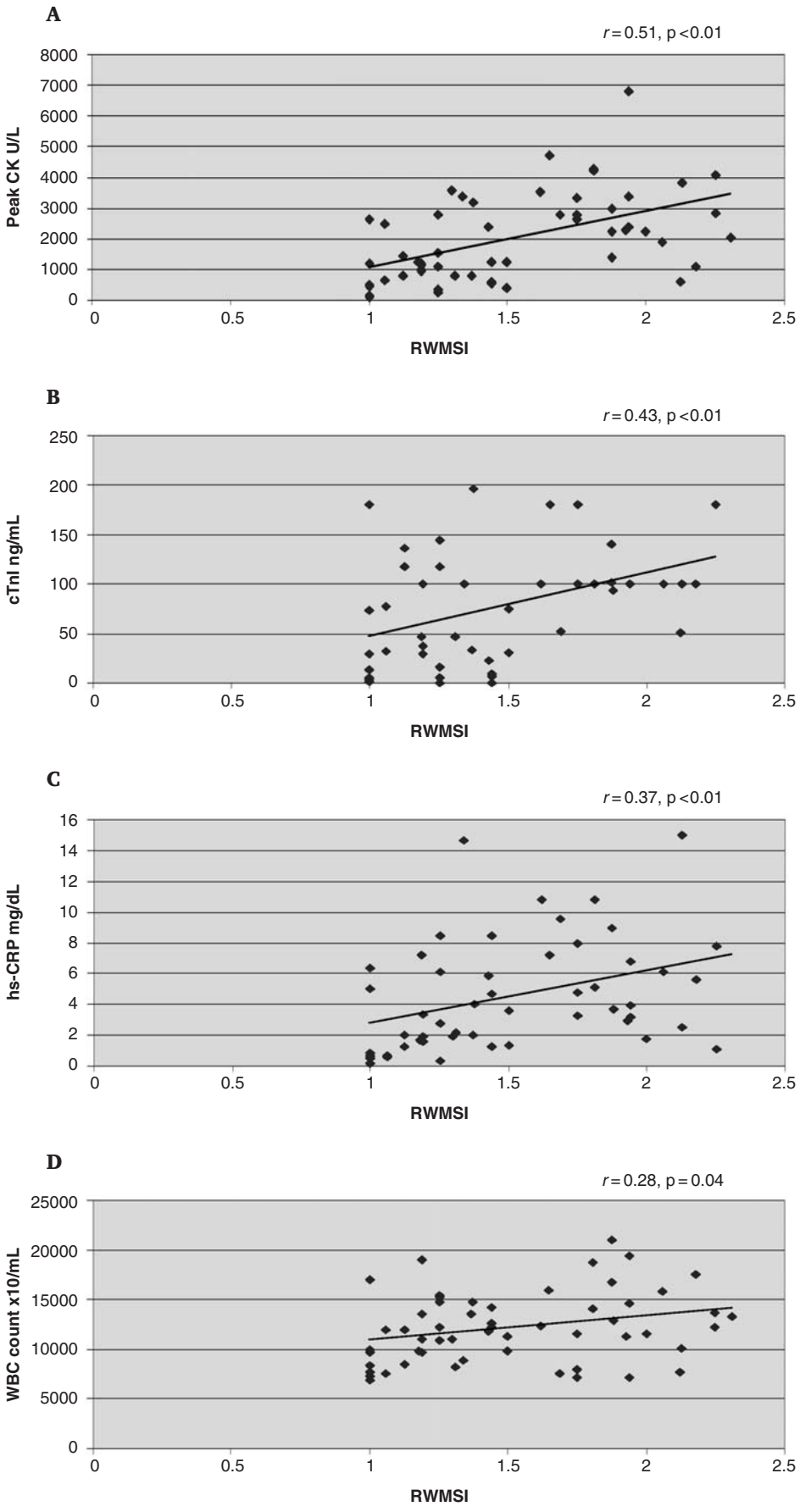
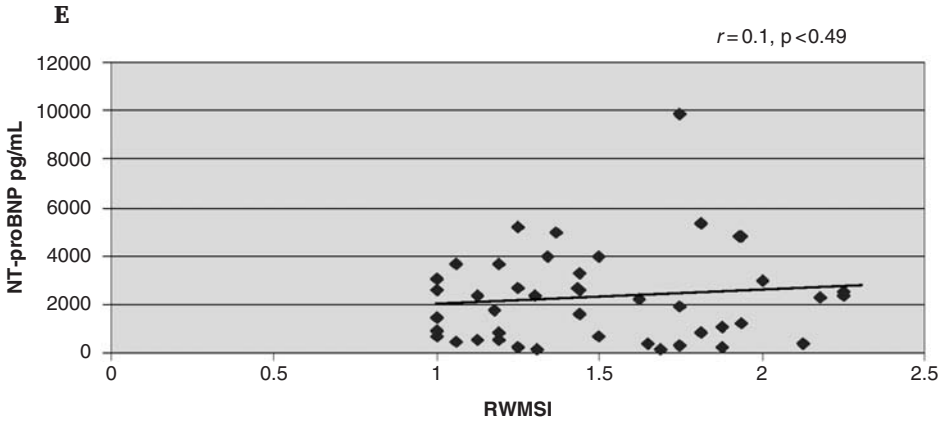


Figure 1.
Correlation between RWMSI and **A.** peak CK (U/L) levels. **B.** cTnI (ng/L) levels. **C.** hs-CRP levels (mg/dL). **D.** WBC count. **E.** NT-proBNP (pg/mL) levels.



multivariate analysis that included age, gender, infarct location, CK levels, cTnI levels, hs-CRP levels, WBC count, and NT-proBNP levels, the only predictor of systolic LV dysfunction was peak CK level ($p < 0.01$). With ROC analysis, peak CK level was the best predictor of systolic LV dysfunction (area under the curve, 0.78, $p < 0.01$).

NT-proBNP and Diastolic Dysfunction

Patients with systolic dysfunction frequently have diastolic dysfunction.[26] In order to examine the association between NT-proBNP levels and diastolic dysfunction, we further evaluated patients with preserved LV function.

Of the 36 patients with preserved systolic LV function, 20 had normal diastolic function and 16 had diastolic dysfunction, all of whom had impaired relaxation (type I diastolic dysfunction). The baseline characteristics of theses 36 patients are presented in Table II.

The only significant association with diastolic dysfunction after STEAMI was increased age ($p < 0.01$). NT-proBNP levels were not higher among patients with diastolic dysfunction (Figure 2). Among patient with diastolic dysfunction, there was no significant correlation between NT-proBNP levels and E/A ratio ($r = 0.19$, $p = 0.18$) (Figure 3A) or E-wave DT ($r = 0.22$, $p = 0.15$) (Figure 3B).

Discussion

Main Findings

The present study in a cohort of patients with a first STEAMI demonstrates that in the early phase after STEAMI, serum concentrations of NT-proBNP were not indicative of systolic or diastolic LV function.

NT-proBNP and Systolic LV Dysfunction

The relationship between BNP or NT-proBNP and LV systolic dysfunction after STEAMI, in previous studies has not been uniform. McClure et al,[16] Omland et al,[17] and Bonini et al[18] reported that NT-proBNP and BNP levels in subacute phase of STEAMI are not useful for detecting LV systolic dysfunction. Usimaa et al[19] reported that BNP at the day of catheterization and 6 months after STEAMI did correlate with LV function. Other studies[20,21] reported that plasma BNP and NT-proBNP levels in the subacute phase of STEAMI were a sensitive means for detecting LV dysfunction. Talwar et al[22] and Horio et al[23] reported that plasma NT-proBNP or BNP measured soon after and remotely after STEAMI predict LV dysfunction. Our study did not find a correlation between early phase NT-proBNP levels and LV systolic function. A possible explanation for the discordance between the different studies could be the timing of measurement of NT-proBNP levels. After STEAMI, BNP levels are elevated immediately and remain elevated for 4 weeks.[23] The time course of the plasma BNP and NT-proBNP levels could be divided into 2 patterns,[22,27] a monophasic pattern with 1 peak at about 16 hours after admission and a biphasic pattern with 2 peaks at about 16 hours and 5 days after admission. Plasma concentrations of BNP reflect the degree of LV dysfunction in the biphasic group. The optimum time of sampling for NT-proBNP following STEAMI for prediction of LV systolic function may be better in the subacute or chronic phase, and not in the early phase after STEAMI.

Table II. Baseline characteristics of patients with preserved systolic LV function.

	Normal Diastolic Function n = 20	Diastolic Dysfunction n = 16
Age, yr	55 (±13)	60 (±7)*
Female sex, %	20	25
Hypertension, %	27	44
Smoking, %	53	50
Diabetes mellitus, %	13	31
Hyperlipidemia, %	71	63
SBP, mm Hg	140 ±28	141 ±19
DBP, mm Hg	74 ±15	79 ±15
Peak CK, U/L	1,617 (±1,430)	1,001 (±807)
CTnI, ng/mL	53 (±60)	56 (±59)
hs-CRP, mg/dL	4.7 (±3.3)	3.3 (±3.6)
NT-ProBNP, pg/mL	1,949 (±1,316)	2,525 (±565)

*$p < 0.05$.
Continuous variable presented as x ± SD.
DBP = diastolic blood pressure, SBP = systolic blood pressure, other abbreviations, see Table I.

NT-proBNP and Diastolic Dysfunction

Patients with diastolic dysfunction frequently have elevated plasma BNP concentrations independently of LV hypertrophy, even after their symptoms are controlled.[28] BNP levels are usually within the normal range among patients with type I diastolic heart failure, and elevated in the advanced forms of diastolic dysfunction—pseudonormal filling and restrictive filling.[25,29,30] There are few data about BNP and NT-proBNP levels and diastolic dysfunction in patient shortly after STEAMI. In 1 report,[31] BNP was found to be accurate in detecting isolated diastolic dysfunction post-STEAMI. In our study the only significant univariable associated with diastolic dysfunction was increased age, reflecting the reported increased prevalence of diastolic heart failure with aging.[32] Hypertensive heart disease and LV hypertrophy are the major underlying cardiovascular diseases in diastolic heart failure.[33]

In our cohort of patients after STEAMI with only impaired relaxation as the manifestation of diastolic dysfunction, diastolic dysfunction could not be accurately diagnosed by measuring pro-BNP levels. We did not measure pulmonary venous flow velocity curves and mitral annular motion, thus possibly misclassifying some patients with pseudo-normal pattern as patients with normal diastolic function. However, this was probably rare in this population, since they were all with normal systolic function, and a restrictive pattern of diastolic dysfunction has usually been observed primarily in patients with an advanced degree of systolic dysfunction.[25]

Summary

Our findings suggest that measurement of serum NT-proBNP concentrations in the early phase of

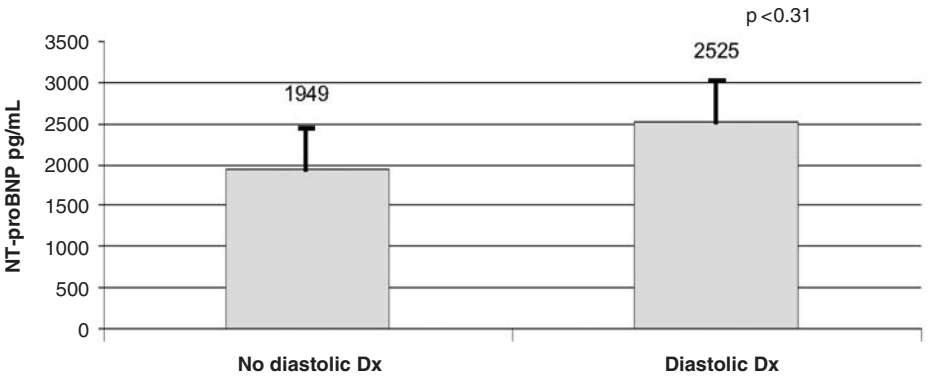


Figure 2.
Mean levels of NT-proBNP (pg/mL) among patients with diastolic dysfunction and patients with normal diastolic function.

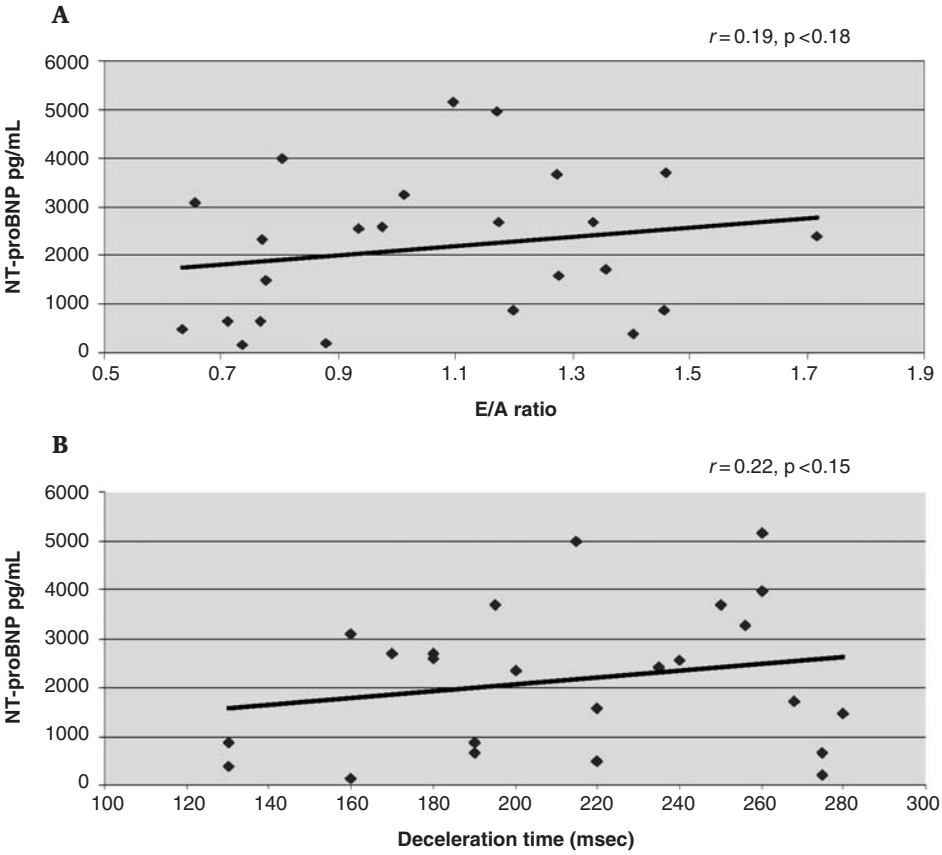


Figure 3.
The correlation between (**A**) E/A ratio and NT-proBNP (pg/mL) levels and (**B**) E-wave DT and NT-proBNP (pg/mL) levels.

STEAMI is not accurate in identifying LV systolic or diastolic dysfunction, and thus does not supplant a thorough echocardiographic examination.

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