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Prediction of left ventricular function in patients after acute myocardial infarction treated with primary angioplasty

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Abstract

Background: *Despite a substantial reduction in in-hospital mortality, the long-term outcomes of patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous transluminal coronary angioplasty (PTCA) remain uncertain. The main causes include progressive left ventricle (LV) remodelling and impaired LV systolic function with a decreased ejection fraction (EF). B-type natriuretic peptide testing has recently emerged as an innovative approach that might enhance the echocardiography-based risk stratification after STEMI. The aims of the study included long-term echocardiographic assessment of LV function and remodelling in patients with STEMI treated with PTCA. Additionally, evaluation of the N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level utility was performed to identify factors at patient discharge which would enable to predict LV dysfunction and remodelling after STEMI at 6-month follow-up.*

Methods: *Echocardiography was performed in 98 patients at discharge and at 6-month follow-up. The diameters of the heart chambers and indices of LV systolic and diastolic function were measured. Plasma levels of NT-proBNP were measured before PTCA and at 6 months.*

Results: *Primary PTCA successfully restored normal epicardial blood flow in the infarct-related Artery (IRA) in 96 patients. At 6 months preserved LV systolic function (median EF 47.5%), decreased LV diastolic function with relaxation abnormalities (E/A < 1.0 and IVRT > 105 ms) and no significant increase in left ventricular end-diastolic diameter (LVEDD)*

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were observed in study population. Multivariate analysis identified low baseline NT-proBNP level, low peak creatine phosphokinase (CPKmax) activity and high EF at discharge as powerful independent predictors of preserved EF at 6 months. LVEDD at discharge, baseline NT-proBNP level and CPKmax correlated with LVEDD at 6 months in the multiple regression model. In multivariate analysis a high NT-proBNP level on admission and low LVEDD at discharge were independent predictors of LVEDD change. Patient groups with reperfusion obtained < and > 3.2 h from symptom onset (the median delay) did not differ with respect to IRA blood flow, infarct size assessed as CPKmax and LVEDD at 6 months. A significant increase in EF was noted only in patients with chest pain duration < 3.2 h. Time-to-treatment correlated with NT-proBNP level at 6 months.

Conclusions: *Successful primary PTCA in STEMI influences LV systolic function improvement and effectively prevents LV remodelling at the 6-month follow-up. Low baseline NT-proBNP, low CPKmax and high EF at discharge are powerful independent predictors of preserved EF after 6 months. A high NT-proBNP level on admission and low LVEDD at discharge predict a propensity for LV remodelling. A prolonged time-to-treatment of STEMI results in a lack of significant long-term improvement in LV systolic function and does not seem to have an impact on the occurrence of LV remodelling.* (Folia Cardiol. 2006; 13: 605–619)

Key words: primary percutaneous transluminal coronary angioplasty, echocardiography, post-infarct left ventricle remodelling, left ventricular systolic and diastolic function, N-terminal pro-brain natriuretic peptide

Introduction

Despite a substantial reduction in in-hospital mortality, the long-term outcomes of patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous transluminal coronary angioplasty (PTCA) remain uncertain [1–3]. The main causes of poor prognosis after STEMI include progressive left ventricle (LV) remodelling with chamber dilation, deformation and impaired LV systolic function with a decreased ejection fraction (EF) of below 40% [4–9]. Moreover, recent studies have demonstrated that LV diastolic dysfunction influences progression of the chamber remodelling and worsens patient prognosis after STEMI, irrespective of impaired LV systolic function [10–13, 67–69].

According to the "open artery" theory, the patency of the infarction-related coronary artery (IRA) plays a major role in LV remodelling following STEMI [14, 15]. The restoration of blood flow in the IRA reduces the extent of tissue necrosis and diminishes infarct expansion, thus improving patient prognosis. The current theory of the "open microvascular bed" states that preservation of LV function after STEMI requires that both complete coronary microvascular reperfusion and sustained IRA and microcirculatory flow be obtained [16, 17]. In the literature there are no unequivocal data indicating that primary PTCA prevents long-term LV dysfunction more effectively than thrombolysis [1, 6, 18–20]. The incidence of LV remodelling in patients after STEMI treated with thrombolysis reaches 35%, with normal IRA flow in 50–60% cases [3, 4, 21]. Studies in patients with STEMI submitted to primary PTCA procedures have shown that, despite complete IRA patency being obtained in 80–95% cases, as many as 30% patients may experience LV dilatation 6 months after infarction [3, 6, 7]. The reason for this may be the lack of blood flow in the coronary microcirculation observed in 30% patients (the no-reflow phenomenon) in spite of the completely restored IRA patency, resulting in more extensive tissue necrosis and a higher incidence of complications [22–27]. Remodelling therefore seems to have a stronger influence on long-term prognosis in patients with STEMI than does IRA patency.

The results of clinical studies have indicated parameters, which, at the moment of discharge from hospital, enable those STEMI patients to be identified who are at high risk of adverse LV remodelling and dysfunction in the long term [18]. Currently the main predictors of LV remodelling after myocardial infarction are as follows: no application of reperfusion therapy, a lack of IRA flow restoration and normal microvascular perfusion after successful primary PTCA, extensive necrosis, particularly in cases of transmural infarction, anterior wall location, symptoms of heart failure at admission,

a restrictive type of transmitral flow in echocardiography and administration of non-steroid anti-inflammatory drugs in the acute phase of STEMI [6, 17, 25, 28]. Among the factors said to favour long-term LV function improvement after STEMI are complete IRA reflow, absence of extensive tissue necrosis and a smaller myocardial perfusion defect in contrast echocardiography after reperfusion [6, 28, 29].

Simple, objective, non-invasive and widely applicable methods of predicting and detecting LV dysfunction and remodelling in patients with STEMI are currently under investigation. Echocardiography is the fundamental tool in the non-invasive assessment of LV morphology and function, although it is not readily available and the investigator requires considerable experience.

Evaluation of the N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level is a useful tool in the detection of asymptomatic LV dysfunction as well as in diagnosing, prognosis assessment and monitoring in symptomatic heart failure [30, 31]. Reports in the literature have raised hopes that NT-proBNP could become a promising risk marker of adverse clinical outcome in patients with STEMI [2, 33–38].

The study presented here was performed in a group of patients with STEMI submitted to primary PTCA. The aims of the study were:

— long-term echocardiographic assessment of LV function and the incidence of LV remodelling;
— evaluation of NT-proBNP plasma level utility in the diagnosis and prediction of LV remodelling and dysfunction at 6-month follow-up;
— attempted identification of the factors which, at the moment of discharge from hospital, enable LV dysfunction and remodelling after STEMI to be predicted.

Methods

Design of the study and characteristics of the study population

The study group consisted of 98 patients (75 men and 23 women) admitted to the Department of Cardiology and Internal Diseases of the Collegium Medicum in Bydgoszcz with a diagnosis of STEMI and designated to undergo primary PTCA procedures. The study enrollment criteria were:

— typical anginal pain for at least 20 minutes;
— symptom onset less than 12 h before admission to hospital and electrocardiographic features of currently evolving STEMI (elevation of ST segment ≥ 0.1 mV in at least two limb leads or ≥ 0.2 mV in at least two precordial leads).

Patients with the following features were excluded:

— a history of previous myocardial infarction;
— prior coronary revascularisation;
— cardiogenic shock at admission;
— bundle branch block;
— persistent atrial fibrillation;
— haemodynamically significant valvular heart diseases;
— idiopathic cardiomyopathies.

The clinical characteristics of the patient population are presented in Table 1. The study protocol was accepted by the Bioethics Committee of the Collegium Medicum in Bydgoszcz. Each patient gave informed consent to participation in the study.

Coronary angiography and percutaneous transluminal coronary angioplasty

Before intervention patients were administered intravenous unfractionated heparin (100 IU/kg), 300 mg clopidrogel and 300 mg acetylsalicylic acid, if the patient had not previously self-administered these. Abciximab (blocker of glycoprotein IIb/IIIa receptor) was administered at the discretion of the invasive cardiologist. Additionally, 75 mg clopidogrel

Table 1. Clinical characteristics of the study population (n = 98).

Age (years)	55.0 (50.0–63.0)
Sex (male/female)	75/23
Infarct location: anterior/inferior/ /lateral wall	55/42/1
Time from symptom onset [h]	3.2 (2.2–4.5)
CPK_{max} [U/l]	1173.5 (451.0–2142.0)
Risk factors of coronary artery disease	
Body mass index [kg/m^2]	26.6 (23.8–28.4)
Arterial hypertension	43 (44%)
Diabetes mellitus	13 (13%)
Current smokers	59 (60%)
History of smoking	23 (23%)
Positive family history	32 (33%)
LDL [mg/dl]	130.5 (104.0–160.0)
HDL [mg/dl]	44.0 (35.4–55.0)
Triglicerydes [mg/dl]	118.0 (90.0–177.0)
Cardiological history	
Angina pectoris preceding infarction	64 (65%)
Medical treatment	
Acetylsalicylic acid	98 (100%)
Statins	97 (99%)
ACE inhibitors	95 (97%)
Beta-blockers	96 (98%)

CPK_{max} — maximal creatine phosphokinease activity in the acute phase of STEMI

or 2 × 250 mg ticlopidine were administered for one month following primary PTCA and 75 mg acetylsalicylic acid daily was prescribed for the lifetime of each patient.

Coronary angiography and primary PTCA procedures were performed using the standard technique via the femoral artery with the aid of the CAS-10A device (Toshiba, Japan). Non-ionic low-osmolar contrast media were applied. The optimal direct effect of the intervention was assigned when no residual stenosis or a stenosis of less than 20% of the reference segment diameter was observed. During angiography at least 5 left coronary artery and 3 right coronary artery projections were taken after a previous administration of 0.3 mg nitroglycerine into the coronary vessels, if arterial pressure was sufficient. Epicardial coronary flow was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) scale and myocardial perfusion according to the TIMI Myocardial Perfusion Grade (TMPG). A reliable evaluation of microvascular perfusion in the area of the STEMI after primary PTCA was obtained in 27 patients.

Echocardiography

Transthoracic echocardiography was performed in each patient on the day of discharge from hospital (d) and after 6 months (f), using the Philips SONOS 2000 and 7500 devices. The diameters of the heart chambers and the following LV function parameters were assessed during each procedure:

— parameters of the LV systolic function — LV ejection fraction (EF, assessed through the summation of discs from the 2 planes in 4-chamber and 2-chamber apical projections) and the index of LV contractility-wall motion score index (WMSI, expressed as the quotient of the scores and the number of assessed segments, using the division of the left ventricle muscle into 16 segments; normokinetic, hypokinetic and dyskinetic segments were assigned scores of 1, 2, 3, and 4 points respectively);
— Doppler parameters of the LV diastolic function — peak velocity transmitral flow in its early phase (E) and during atrial systole (A); the E/A ratio; deceleration time (DT) of the early transmitral flow, and the isovolumetric relaxation time (IVRT).

An increase in left ventricle end-diastolic diameter (LVEDD) of at least 10% at 6 months was accepted as a marker of LV remodelling. An improvement in LV systolic function at the 6-month follow-up was defined by statistically significant changes in the following echocardiographic parameters: an EF increase and/or a WMSI decrease. Diastolic LV dysfunction of the disturbed relaxation pattern was diagnosed when the E/A ratio was lower than one, and IVRT was greater than 105 ms. A restrictive pattern of transmitral flow was assigned when the E/A ratio was greater than 2 and the DT shorter than 130 ms.

Laboratory tests

NT-proBNP plasma level was evaluated at baseline before primary PTCA (NT-proBNPd) and at 6 months after STEMI (NT-proBNPf) through ECLIA electrochemiluminescent assay (ELECSYS 1010 device, Roche Diagnostics, Mannheim, Germany).

Statistical analysis

Calculations were performed using the Polish version of the Statistica 7.1 software (StatSoft, Tulsa, USA). The usage of the Kolmogorov-Smirnov test demonstrated that the analysed quantitative variables were not normally distributed. Therefore, quantitative variables were expressed as median values and quartile ranges. Suitable non-parametric tests (Mann-Whitney, Kruskal-Wallis and Wilcoxon) were used for comparison of median values from quantitative dependent and independent variables. For evaluation of correlations between significant quantitative variables Spearman's correlation coefficient and test of significance for this coefficient were used. Qualitative variables were expressed as the number of patients presenting the given feature and the percentage of patients in the group analysed. Unrelated qualitative variables were compared using the χ^2 test with Yeats's correction when suitable or the accurate Fisher test. Analysis of related qualitative variables was performed using the McNamara test. The influence of numerous variables upon a quantitative variable was assessed using the multiple regression model. Four digits after the decimal point were presented for the accuracy of the p-value. Values of p below 0.05 were statistically significant. Accurate p-values were presented from within the range of 0.05–0.10 with a trend toward statistical significance, whereas p-values over 0.10 were treated as non-significant and marked "NS".

Results

Before primary PTCA procedures grade 0 or 1 flow according to the TIMI scale was observed in the IRA in 69 patients (70%) (the left anterior descending artery in 57% patients, left circumflex

artery in 7% and right coronary artery in 36% patients). Successful primary PTCA interventions were performed in all the patients studied, resulting in TIMI grade 3 flow in the IRA in 96 individuals (98%). Multivessel lesions were found in 45 patients (46%). In 63 (64%) abciximab was administered and in 89 (91%) coronary stents were implanted. Perfusion of the microcirculatory bed in the area of the STEMI after primary PTCA was described as grade 2 or 3 in the TMPG scale in 52% patients.

During the 6-month follow-up period one decease (1%) occurred and 2 cases of myocardial infarction (2%) were noted, and in 6 patients (6%) repeated coronary angioplasty was performed. An insignificant increase in NT-proBNP plasma level from 309.3 pg/ml (114.1–1226.5) to 344.5 pg/ml (167.6–596.9) was observed during the follow-up period.

The echocardiographic characteristics of the study population on the day of discharge and at 6 months from STEMI are presented in Table 2. On the day of discharge the following findings were noted in the study group: increased diameter of the left atrium (LA), normal LVEDD, no significant impairment of LV contractility (EF of 45.0%) and a lack of reliable evidence of significant diastolic dysfunction of the LV (normal E/A ratio, slight prolongation of IVRT, no significant DT shortening). After the 6-month follow-up period a significant increase in EF and IVRT prolongation were observed as well as a significant decrease in WMSI and the E/A ratio with no significant changes in LVEDD and LA. Analysis of echocardiographic parameters at 6 months in the group of patients studied revealed preserved systolic LV function and abnormal diastolic LV function in the form of an impaired relaxation pattern (Table 2). At 6 months patients with median or lower NT-proBNPd levels (i.e. ≤ 309.3 pg/ml) demonstrated a significant decrease in WMSI (1.59 *vs.* 1.43 points; p = 0.0041), an increase in EF (45.0% *vs.* 50.0%; p = 0.002) and a lower E/A ratio (1.21 *vs.* 0.97; p = 0.0068). On the other hand, patients with NT-proBNPd levels greater than the median value (i.e. > 309.3 pg/ml) had an increased LVEDD (50.0 *vs.* 51.5 mm; p = 0.0964), significant IVRT prolongation (112 *vs.* 119.5 ms; p = 0.0117), a lower E/A ratio (0.92 *vs.* 0.88; p = 0.0985) and no significant changes in EF and WMSI. After 6 months of follow-up patient groups with NT-proBNPd levels lower/equal to or greater than the median value had a significantly different EF (50.0% *vs.* 45.5%; p = 0.0176) and LA diameter (40.5 mm *vs.* 42.0 mm; p = 0.0830). At 6 months after intervention patients with NT-proBNPd levels ≤ 309.3 pg/ml had a significantly higher EF than those with NT-proBNPd > 309.3 pg/ml; there was no difference in EF between the two groups on the day of discharge (45.0% *vs.* 44.0%; p = NS). After follow-up the EF was significantly greater and the WMSI lower in the group of patients with NT-proBNPf lower/equal to median value (≤ 344.5 pg/ml) as compared to the group with NT-proBNPf greater than the median value (50.0% *vs.* 45.0%; p = 0.0013 and 1.42 *vs.* 1.60; p = 0.0004, respectively). The latter group had a greater LVEDD and left ventricular end-systolic diameter (LVESD) after 6 months (49.5 *vs.* 54.0 mm; p = 0.0145 and 30.0 *vs.* 36.0 mm; p = 0.0000, respectively).

Univariate analysis demonstrated the following significant negative correlations: NT-proBNPd and EFf (R_S = –0.2877; p = 0.0072) (Fig. 1); NT-proBNPf and EFd and EFf (R_S = –0.28 and R_S = –0.41; p = 0.0072 and p = 0.0001, respectively) (Fig. 2), and DTd and DTf (R_S = –0.33 and R_S = –0.21; p = 0.0021 and p = 0.0552, respectively) (Fig. 3). Additionally, positive correlations were found between NT-proBNPf and LVEDDf (R_S = 0.2356; p = 0.0270) and between WMSId (R_S = 0.2743; p = 0.0101) and WMSIf (R_S = 0.4310; p = 0.0000). Multivariate analysis revealed that independent predictors of the EFf value were maximal creatine phosphokinase

Table 2. Echocardiographic characteristics of the study population.

LAd [mm]	41.0 (38.5–45.0)	NS
LAf [mm]	41.0 (38.0–44.0)	
LVEDDd [mm]	51.0 (48.5–55.0)	NS
LVEDDf [mm]	51.0 (48.0–57.0)	
LVESDd [mm]	32.0 (29.0–37.5)	NS
LVESDf [mm]	33.0 (30.0–38.0)	
WMSId [pts]	1.60 (1.42–1.81)	0.0005
WMSIf [pts]	1.44 (1.31–1.69)	
LVEFd [%]	45.0 (40.0–50.0)	0.0027
LVEFf [%]	47.5 (43.0–53.0)	
E/Ad (–)	1.1884 (0.8133–1.3966)	0.0015
E/Af (–)	0.9136 (0.7595–1.1940)	
DTd [ms]	147.0 (129.0–172.0)	NS
DTf [ms]	144.0 (130.0–165.0)	
IVRTd [ms]	112.0 (100.0–129.5)	0.0085
IVRTf [ms]	120.0 (110.0–130.0)	

LA — diameter of left atrium; LVEDD — end-diastolic diameter of left ventricle; LVESD — end-systolic diameter of left ventricle; WMSI — wall motion score index of left ventricle; LVEF — left ventricular ejection fraction; E — peak velocity of early transmitral flow; A — peak velocity of transmitral flow during atrial systole; DT — deceleration time of the early transmitral flow; IVRT — isovolumetric relaxation time; d —parameter value at patient discharge; f — parameter value after the 6-month follow-up period

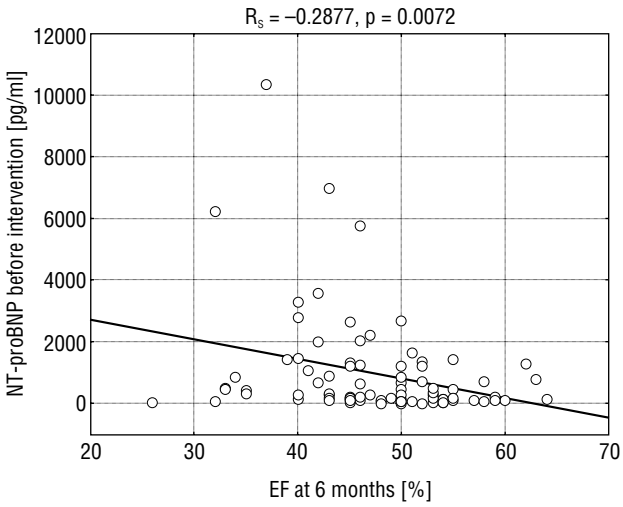

Figure 1. Relation between baseline N-terminal pro-brain natriuretic peptide level (NT-proBNP) and left ventricular ejection fraction (EF) at 6 months after intervention.

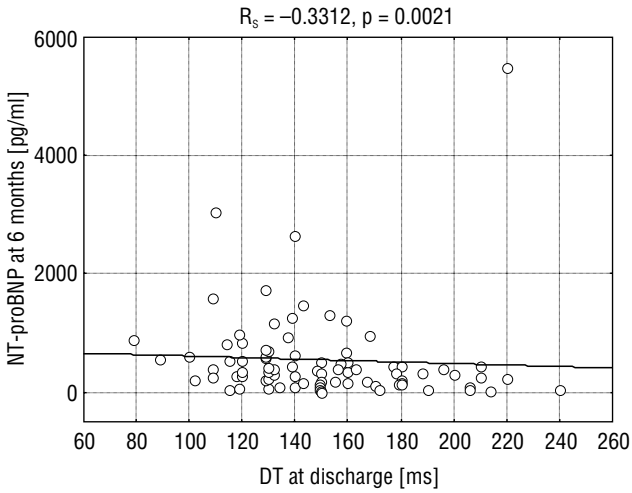

Figure 3. Relation between deceleration time (DT) at discharge and N-terminal pro-brain natriuretic peptide level (NT-proBNP) at 6 months after intervention.

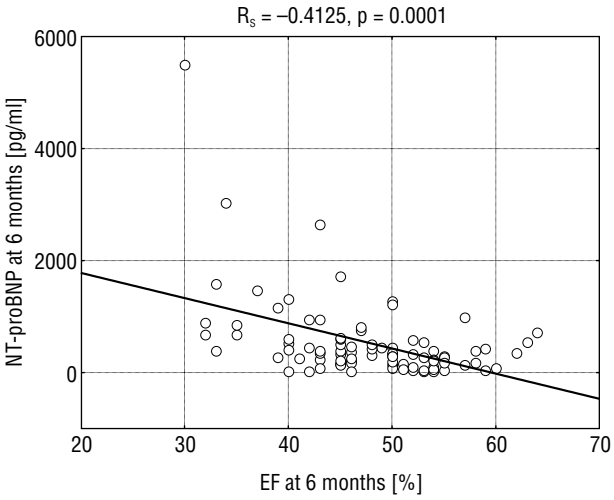

Figure 2. Relation between N-terminal pro-brain natriuretic peptide level (NT-proBNP) and left ventricular ejection fraction (EF), both at 6 months after intervention.

(CPK_{max}) and NT-proBNPd (an inversely proportional relation) as well as EFd (directly proportional) (Table 3). Independent predictors of LVEDDf value were $CPK_{max,}$ NT-proBNPd and LVEDDd (directly proportional relations for each variable) (Table 4).

Independent predictors of increase in ΔLVEDD after 6 months include LVEDDd (inversely proportional) and NT-proBNPd (directly proportional) (Table 5). When patient groups were compared in relation to ΔLVEDD after 6 months (≤ – 10%, n = 11; > – 10% and < 10%, n = 69; ≥ 10%, n = 13), no significant differences were found between the extent of tissue necrosis assessed through enzymatic activity (CPK_{max} of 1080.0 U/l *vs.* 1184.0 U/l *vs.* 1644.0 U/l; p = NS) and between different time spans from pain onset to reperfusion (4.0 h *vs.* 3.1 h *vs.* 2.3 h; p = NS). Patients with the greatest LV dilatation after 6 months (≥ 10%) also had the highest NT-proBNPd values of 508.1 pg/ml (114.7; 1458.0). A significant difference in NT-proBNPd was observed between the groups with ΔLVEDD ≤ –10%, > –10% and < 10%. Moreover, higher NT-proBNPd was noted in the group of patients with ΔLVEDD ≥ 10% as compared to the group with ΔLVEDD ≤ – 10% after 6 months (Fig. 4). The highest levels of NT-proBNPf, reaching 715.9 pg/ml (267.3; 1525.5), were observed in patients with the greatest LV dilatation after 6 months. A trend towards higher levels of NT-proBNPf was found in patients with ΔLVEDD ≥ 10% as compared to those with ΔLVEDD > –10% and < 10% after 6 months (Fig. 5). Patients with the greatest LV dilatation on follow-up demonstrated a significantly higher LAf, LVESDf, WMSId and WMSIf and the lowest values for EFd and EFf (Table 6).

A comparison of the patient groups with the time from symptom onset to reperfusion lower/ /equal to the median value (i.e. ≤ 3.2 h; n = 48; most often STEMI of the anterior wall) with those with time-to-treatment greater than the median (> 3.2 h; n = 49) revealed no significant differences in primary PTCA efficacy in restoring IRA flow (grade 2 or 3 in the TIMI scale: 48 *vs.* 49 patients, respectively; p = NS) and in enzymatic assessment of the extent of necrosis (CPK_{max} of 1134.0 U/l *vs.* 1184.0 U/l, respectively; p = NS). NT-proBNPd levels both at discharge and at follow-up were higher in patients with

Table 3. Impact of variables from Tables 1 and 2 and baseline NT-proBNP level on LVEF after 6 months in the multiple regression model.

	Beta coefficient	Beta coefficient standard error	Direction component beta	Beta coefficient standard error	p
Entire study population (n = 93)					
Model characteristics: R = 0.4437; R^2 = 0.1969; p = 0.0001					
Free term			51.4493	1.1741	0.0000
CPK_{max} [U/l]	–0.3387	0.0988	–0.0016	0.0005	0.0009
NT-proBNPd [pg/ml]	–0.3185	0.0988	–0.0014	0.0004	0.0018
Model including EF value at discharge					
Model characteristics: R = 0.7695; R^2 = 0.5921; p = 0.0000					
Free term			20.1182	3.6847	0.0000
CPK_{max} [U/l]	–0.1909	0.0736	–0.0009	0.0003	0.0112
NT-proBNPd [pg/ml]	–0.1734	0.0735	–0.0008	0.0003	0.0208
LVEFd [%]	0.6529	0.0751	0.6466	0.0744	0.0000

CPK_{max} — maximal creatine phosphokinease activity in the acute phase of STEMI; NT-proBNP — N-terminal pro-brain natriuretic peptide; LVEF — left ventricular ejection fraction; d — parameter value at patient discharge

Table 4. Impact of variables from tables 1 and 2 and baseline NT-proBNP level on LVEDD after 6 months in the multiple regression model.

	Beta coefficient	Beta coefficient standard error	Direction component beta	Beta coefficient standard error	p
Entire study population (n = 93)					
Model characteristics: R = 0.3425; R^2 = 0.1173; p = 0.0056					
Free term			49.67848	0.988597	0.000000
CPK_{max} [U/l]	0.238100	0.103541	0.00090	0.000393	0.023984
NT-proBNPd [pg/ml]	0.268425	0.103541	0.00098	0.000377	0.011258
Model including LVEDD value at discharge					
Model characteristics: R = 0.7004; R^2 = 0.4906; p = 0.0000					
Free term			11.8552	4.9696	0.0194
CPK_{max} [U/l]	0.1577	0.0803	0.0006	0.0003	0.0530
NT-proBNPd [pg/ml]	0.2150	0.0799	0.0008	0.0003	0.0087
LVEDDd [mm]	0.6179	0.0802	0.7483	0.0971	0.0000

CPK_{max} — maximal creatine phosphokinease activity in the acute phase of STEMI; NT-proBNP — N-terminal pro-brain natriuretic peptide; LVEDD — end-diastolic diameter of left ventricle diameter; d — parameter value at patient discharge

a duration of infarct pain of over 3.2 h than in those experiencing symptoms for ≤ 3.2 h (NT-proBNPd of 510.9 pg/ml *vs.* 208.7 pg/ml, respectively; p = 0.0677; NT-proBNPf of 233.9 pg/ml *vs.* 131.3 pg/ml; p = 0.0864). Univariate analysis revealed a significant positive correlation between the duration of pain to the moment of reperfusion and NT-proBNPf level (R_S = 0.2640; p = 0.0135) as well as a trend toward significance concerning NT-proBNPd (R_S = = 0.1824; p = 0.0835). A significant EF increase after follow-up was noted exclusively in the group of patients with pain duration shorter than the median (though the difference in EFf between the groups was not significant and in both groups the value of the EFf was greater than 45%) (Table 7). A significant decrease in the E/A ratio after 6 months was observed only in patients with pain duration longer than the median (though the difference in E/Af between the groups was not significant and both groups the valve of E/Af was lower than one) (Table 7).

Table 5. Impact of variables from Tables 1 and 2 and baseline NT-proBNP level on LVEDD after 6 months in the multiple regression model.

	Beta coefficient	Beta coefficient standard error	Direction component beta standard	Beta coefficient error	p
Entire study population (n = 93)					
Model characteristics: R = 0.2385; R^2 = 0.0569; p = 0.0279					
Free term			–0.015628	0.580939	0.978604
NT-proBNPd [pg/ml]	0.238535	0.106596	0.000675	0.000302	0.027916
Model including LVEDD value at discharge					
Model characteristics: R = 0.3387; R^2 = 0.1147; p = 0.0068					
Free term			11.6090	5.0538	0.0241
NT-proBNPd [pg/ml]	0.2566	0.1042	0.0007	0.0003	0.0159
LVEDDd [mm]	–0.2412	0.1042	-0.2268	0.0980	0.0231

NT-proBNP — N-terminal pro-brain natriuretic peptide; LVEDD — end-diastolic diameter of left ventricle diameter; d — parameter value at patient discharge

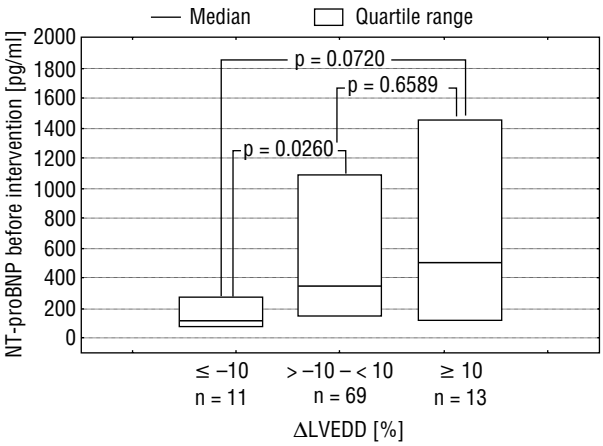

Figure 4. Comparison of baseline N-terminal pro-brain natriuretic peptide levels (NT-proBNP) in patient groups in relation to left ventricular end-diastolic diameter (ΔLVEDD) change at 6 months after intervention.

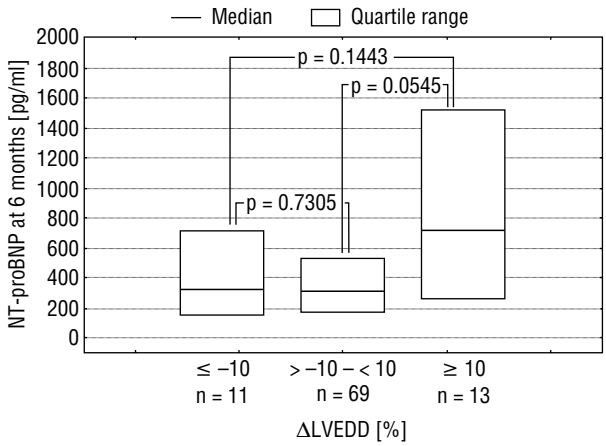

Figure 5. Comparison of N-terminal pro-brain natriuretic peptide levels (NT-proBNP) at 6 months in patient groups in relation to left ventricular end-diastolic diameter (ΔLVEDD) change at 6 months after intervention.

Discussion

In their study Bolognese et al. [6] observed at long-term follow-up adverse LV remodelling after STEMI in 30% patients submitted to primary PTCA interventions, despite successful IRA patency restoration. This finding is comparable to the incidence in LV remodelling in 34% patients who received thrombolysis in the course of the GUSTO trial [8, 39, 40]. In the group of patients with STEMI undergoing successful primary PTCA presented here the significant LV dilatation was no observed at 6 months after intervention, and an LVEDD increase of ≥ 10% as compared to the value on the day of discharge was noted in 14% patients only. Wita et al. [28] observed adverse LV remodelling after 6 months in as many as 42.2% patients with STEMI of the anterior wall successfully treated with primary PTCA within 12 h of pain onset. The relatively high incidence of LV remodelling after STEMI treated with primary PTCA, resulting in the complete flow restoration in the IRA, reported by the above-mentioned authors in comparison with the results of the present study indicates the influence of additional factors, including selection of patient groups with more extensive tissue necrosis (STEMI of the anterior wall) [6, 28, 41], a lower baseline EF [6, 28, 41] and longer duration of pain until reperfusion [6, 28]. The importance of infarct extent in risk stratification of LV remodelling is

Table 6. Comparison of selected echocardiographic parameters in patient groups in relation to LVEDD change at 6 months after intervention.

Parameter	ΔLVEDD ≤ –10% (n = 11)	–10% < ΔLVEDD < 10% (n = 69)	ΔLVEDD ≥ 10% (n = 13)	p
LAd [mm]	41.0 (36.0–42.0)	41.0 (38.0–44.0)	42.0 (40.0–46.0)	NS
LAf [mm]	42.0 (36.0–44.0)	41.0 (37.0–43.0)	45.0 (42.0–51.0)	0.0060
LVEDDd [mm]	51.0 (51.0–55.0)	52.0 (49.0–55.0)	50.0 (46.0–52.0)	NS
LVEDDf [mm]	46.0 (43.0–48.0)	51.0 (48.0–56.0)	58.0 (57.0–60.0)	0.0000
LVESDd [mm]	31.0 (29.0–35.0)	32.0 (29.0–38.0)	32.0 (28.0–34.0)	NS
LVESDf [mm]	30.0 (27.0–33.0)	33.5 (30.0–37.0)	40.0 (33.0–44.0)	0.0092
WMSId [pts]	1.31 (1.25–1.60)	1.60 (1.42–1.81)	1.71 (1.58–1.81)	0.0226
WMSIf [pts]	1.38 (1.31–1.44)	1.44 (1.31–1.69)	1.60 (1.58–1.83)	0.0077
LVEFd [%]	48.0 (45.0–56.0)	45.0 (40.0–50.0)	40.0 (37.0–45.0)	0.0214
LVEFf [%]	48.0 (45.0–59.0)	49.0 (43.0–53.0)	45.0 (40.0–48.0)	NS
E/Ad (–)	1.2222 (0.8929–1.3877)	1.2002 (0.8125–1.5781)	0.9263 (0.7272–1.2727)	NS
E/Af (–)	1.1940 (0.7595–1.3019)	0.9205 (0.7609–1.1895)	0.8261 (0.7529–0.9750)	NS
DTd [ms]	143.0 (114.0–200.0)	143.5 (129.0–167.0)	150.0 (140.0–180.0)	NS
DTf [ms]	143.0 (140.0–170.0)	146.0 (130.0–165.0)	140.0 (130.0–172.0)	NS
IVRTd [ms]	110.0 (100.0–133.0)	112.0 (100.0–122.0)	120.0 (92.0–130.0)	NS
IVRTf [ms]	130.0 (112.0–150.0)	120.0 (110.0–131.5)	112.0 (104.0–130.0)	NS

LA — diameter of left atrium; LVEDD — end-diastolic diameter of left ventricle diameter; LVESD — end-systolic diameter of left ventricle diameter; WMSI — wall motion score index of left ventricle; LVEF — left ventricular ejection fraction; E — peak velocity of early transmitral flow; A — peak velocity of transmitral flow during atrial systole; DT — deceleration time of the early transmitral flow; IVRT — isovolumetric relaxation time; d — parameter value at patient discharge; f — parameter value after the 6-month follow-up period

Table 7. Comparison of selected echocardiographic parameters in patient groups in relation to time--treatment change at 6 months after intervention

Parameter	Pain duration ≤ median Pain duration ≤ 3.2 hours	p	Pain duration > median Pain duration > 3.2 hours	p	p between groups
LAd [mm]	41.0 (38.0–44.0)	NS	41.5 (38.5–46.0)	NS	NS
LAf [mm]	41.0 (38.0–43.0)		41.5 (38.0–45.0)		NS
LVEDdd [mm]	51.0 (48.0–56.0)	NS	51.0 (48.5–54.0)	NS	NS
LVEDDf [mm]	53.0 (48.0–57.0)		50.0 (48.0–57.0)		NS
LVESDd [mm]	33.0 (29.0–38.0)	NS	31.5 (29.0–36.5)	NS	NS
LVESDf [mm]	34.0 (29.5–38.5)		32.5 (30.0–37.0)		NS
WMSId [pts]	1.60 (1.42–1.81)	0.0061	1.58 (1.40–1.75)	0.0445	ns
WMSIf [pts]	1.50 (1.31–1.75)		1.44 (1.31–1.60)		NS
LVEFd [%]	45.0 (39.0–48.0)	0.0006	46.0 (41.5–50.0)	NS	0.0758
LVEFf [%]	46.0 (43.0–52.0)		49.0 (43.0–54.0)		NS
E/Ad (–)	1.0249 (0.778–1.2727)	NS	1.3303 (0.8929–1.600)	0.0018	0.0486
E/Af (–)	0.9136 (0.7529–1.1935)		0.9091 (0.7595–1.200)		NS
DTd [ms]	150.0 (130.0–179.0)	NS	140.0 (120.0–163.0)	NS	NS
DTf [ms]	144.0 (130.0–167.0)		145.0 (130.0–165.0)		NS
IVRTd [ms]	115.0 (100.0–130.0)	0.0157	112.0 (100.0–127.0)	NS	NS
IVRTf [ms]	130.0 (105.0–137.0)		120.0 (110.0–130.0)		NS

LA — diameter of left atrium; LVEDD — end-diastolic diameter of left ventricle; LVESD — end-systolic diameter of left ventricle; WMSI — wall motion score index of left ventricle; LVEF — left ventricular ejection fraction; E — peak velocity of early transmitral flow; A — peak velocity of transmitral flow during atrial systole; DT — deceleration time of the early transmitral flow; IVRT — isovolumetric relaxation time; d — parameter value at patient discharge; f — parameter value after the 6-month follow-up period

emphasised by the fact that in the reports cited patients with LV remodelling had higher values for the parameters characterising myocardial necrosis [6, 28, 41], although these differences were insignificant in the present study. We demonstrated a significantly worse systolic function of the LV at discharge from hospital and after 6 months in patients who experienced LV remodelling on follow-up (as compared to the group with no signs of such a phenomenon). Nagaya et al. [41] stated that EF and CPK_{max} correlate with LV remodelling 30 days after infarction. Similarly, in his analysis of patients with anterior wall STEMI treated with primary PTCA, Katayama et al. [42] observed a higher incidence of LV remodelling in patients with lower baseline EF and diabetes. In the reports of Bolognese et al. [6] and Wita et al. [28] LV remodelling occurred only in patients with an initial EF value below 40%. We found no relation between diabetes and adverse LV remodelling in the observed population. It should be noted, however, that only 13 patients in the study group had diabetes.

Despite the finding in one study of post-infarct LV dilatation in 30% patients in whom intervention took place within 6 h of pain onset [6], there are emerging reports suggesting that a longer time to invasive treatment has a significant influence on the occurrence of LV remodelling following STEMI [10, 20, 43]. For thrombolytic therapy a linear dependence was demonstrated between the time to the advent of treatment, its angiographic effect and the prognosis in patients with STEMI [40]. No advantage of invasive treatment over fibrinolysis in the prevention of LV remodelling after STEMI was observed when the time from symptom onset was less than 3 h [20] and when the delay in coronary intervention as compared to fibrinolysis was over 60 min [44, 45]. Some authors emphasise that a longer time to reperfusion may have a powerful impact upon LV function and dilatation in patients with STEMI successfully treated with primary PTCA within 3–12 h of the onset of infarct pain [1, 2, 20, 23, 46–48]. Araszkiewicz et al. [49] demonstrated that early primary PTCA intervention (up to 220 min after pain onset) in patients with STEMI of the anterior wall significantly reduces the risk of LV remodelling in the 6 months after infarction. This finding indicates a decreasing LV volume in patients with pain duration until reperfusion of less than 3 h as compared to those treated more than 6 h afterwards, in whom the chamber volume increases [49]. Sheiban et al. [47] found no significant differences in the incidence of LV remodelling when patients with STEMI were successfully treated with primary PTCA not later than 2 h after symptom onset. In the present study no significant relationship was found between duration of infarct pain and indices of LV remodelling. This observation could be influenced by a short mean time to reperfusion (median of 3.2 h) and the fact that only 6 patients in the population described were submitted to primary PTCA after more than 6 h. Several other factors mentioned in the literature could also be beneficial in the progress of LV remodelling in our study. These are TIMI 3 flow in the IRA before primary PTCA, found in 19% patients [36, 50, 51], the occurrence of angina pectoris before STEMI [52] and the wide administration of agents known for their anti-remodelling action, including ACE inhibitors and β-blockers.

Both Bolognese et al. [6] and Wita et al. [28] demonstrated that patients with LV remodelling experienced severe cardiovascular complications significantly more often in long-term follow-up, including death, a further myocardial infarction or an in-hospital stay due to heart failure. The low incidence of LV remodelling, short reperfusion delay, complete IRA patency restoration, preservation of systolic function and an absence of important diastolic LV disturbances could be the reasons for the low incidence of the above-mentioned complications in our patient population at 6 months after STEMI. Other factors concerning primary PTCA intervention which could decrease the incidence of IRA reocclusion and restenosis and influence clinical outcomes in the long term in the group of patients presented include a high rate of coronary stent implantation (91%) and wide administration of abciximab (64%) [22, 36, 52–54]. However, in his study, despite administration of GP IIb/IIIa receptor blockers in 71% and IRA stent implantation in 99% patients, Wita et al. [28] noted a higher mortality at 6 months (3%) and significant IRA restenosis in 36% persons in follow-up coronary angiography performed after 6 months.

The study presented here supports the hypothesis that successful IRA patency restoration through primary PTCA in patients with STEMI enables LV systolic function to be preserved at the time of discharge and improved in the 6 months following acute myocardial infarction. This could result from great primary PTCA efficacy in restoring IRA patency and thus in decreasing the extent of necrosis, reversion of myocardial stunning and restoration of the hibernated myocardial function [28]. Acording to our results CPK_{max} activity is a feature of great importance in predicting deterioration in LV systolic function at 6 months after infarction.

Many authors emphasise that a longer time to reperfusion has a strong influence on LV dysfunction in patients with STEMI submitted to primary PTCA [46, 47, 55]. Such a relationship was observed by Antoniucci et al. [56] in the group of high risk patients (STEMI of the anterior wall, cardiogenic shock on admission, heart rate over 100/min, age over 70 years). De Luca et al. [57] demonstrated that primary PTCA delay in STEMI correlates with worse myocardial perfusion, a greater infarct area and a higher mortality rate after one year. Araszkiewicz et al. [49] found a significantly higher EF both 3 days and 6 months following STEMI in patients with anterior wall infarction submitted to invasive treatment before 3 h from pain onset as compared to those treated after more than 6 h. The present study confirms that early (before 3.2 h) primary PTCA treatment of STEMI makes an important contribution to the improvement of the LV systolic function in long-term follow-up. Our observations are compatible with the results published by Agati et al. [55], who showed that in cases of delayed reperfusion through primary PTCA there may be no improvement in LV systolic function but the beneficial effect of intervention on LV remodelling may be preserved. This observation may result from a different time of evolution of subendocardial and subepicardial necrosis, which may lead to infarct expansion and LV remodelling in cases of a long occluded segment [55].

In the present study, patients with lower NT-proBNP levels after 6 months had lesser adverse post-infarct LV remodelling. LV dilatation in long-term follow-up occurred only in patients with NT-proBNP levels greater than the median value (over 344.5 pg/ml) at 6 months. These patients experienced no improvement in LV systolic function either. The above-mentioned findings confirm the significant relations existing between LVEDD and NT-proBNP, both measured after 6 months. This finding is of great importance with regard to data from the literature which emphasise the occurrence of a second BNP peak or sustained BNP increase (over 3–4 weeks after STEMI) in the development of LV remodelling [58, 59] or LV systolic dysfunction [60] in long-term follow-up. Nagaya et al. [59] described patients with STEMI and a persistent increase in BNP level at 7 days after infarction as the population at highest risk of LV remodelling at 6 months. Nilsson et al. [61] demonstrated that a persistent high level of plasma NT-proBNP is the strongest predictor of remodelling after one year from the acute myocardial infarction [60]. During the 6-month follow-up period of patients with STEMI Wita et al. [28] found greater NT-proBNP levels after 5 days in individuals with adverse LV remodelling; univariate analysis showed a correlation between this feature and the occurrence of remodelling. Nagaya et al. [41] demonstrated that only BNP plasma level assessed on the day of discharge and evaluation of CPK and EF in the acute phase of infarction correlate with LV remodelling 30 days after infarction. A relationship between an increased NT-proBNP plasma level at the time of admission to hospital and the risk of remodelling was found both in patients with STEMI receiving thrombolysis [32] and in those undergoing primary PTCA [62, 63]. Grabowski et al. [64] observed a greater incidence of the no-reflow phenomenon in patients with STEMI submitted to primary PTCA in whom high levels of plasma NT-proBNP were found at admission. Multivariate analysis in the present study demonstrated that NT-proBNP level on admission and LVEDD on discharge in patients with STEMI undergoing primary PTCA constitute an important and independent predictor of adverse LV remodelling at 6 months.

We demonstrated that both baseline NT-proBNP levels and those measured after 6 months in patients with STEMI submitted to primary PTCA significantly correlate with EF value in long-term follow-up. Moreover, improved LV systolic function at 6 months after STEMI was observed exclusively in patients with lower baseline NT-proBNP plasma levels (below 309.0 pg/ml). Patients with a NT-proBNP level lower than the median value (344.5 pg/ml) at 6 months had significantly better systolic function in the long term. The results presented are compatible with the report from Richards et al. [33], who demonstrated a close relationship between BNP plasma levels on days 1–4 of the in-hospital stay and the EF value in the acute phase of STEMI (day 1–4) as well as at 3–5 months after infarction [33]. Other authors have also observed a negative correlation between BNP plasma level and EF [28]. Clinical studies in patients with STEMI have demonstrated the prognostic value of decreased EF. However, there is still no certainty that it is the best predictor of mortality and symptomatic heart failure. Richards et al. [43] performed an analysis on 666 patients with acute myocardial infarction treated in the majority of cases by thrombolysis. They found that increased BNP levels and an EF below 40% are of independent prognostic value for a 3-year risk of decease, heart failure and myocardial infarction. It is noteworthy that BNP was an important and independent predictor of death and heart failure in the subgroup with preserved LV systolic function

(EF over 40%) and that at the same time the EF value had no prognostic importance [43]. To sum up, the NT-proBNP plasma level on admission to hospital may in clinical practice predict the occurrence of remodelling and decreased LV systolic function in patients with STEMI submitted to primary PTCA in whom the EF on the day of discharge is normal.

On the basis of the results of the present study, it has been demonstrated that in patients with STEMI the following are the most important independent predictors of the LV systolic function in the long term: EF on discharge, maximal CPK activity in the acute phase of STEMI and NT-proBNP level before primary PTCA. In the study of Bolognese et al. [6] predictors of LV remodelling included high CPK activity, multivessel disease and abnormal baseline LV systolic parameters. In our study, in contrast, these features played no part in the model of LV remodelling prediction. Among numerous evaluated parameters, Wita et al. [28] described the following as independent markers: proximal occlusion of the left anterior descending coronary artery, no resolution of ST elevation in ECG and high CK-MB levels but not a low EF. Both authors emphasise the role of disturbances in the microvascular coronary bed in the prediction of adverse LV remodelling after infarction [17, 28]. Bolognese et al. [17] reported that the most important factor predicting LV dilatation, decease or propensity for adverse cardiovascular incidents (such as a further infarction or heart failure) over a 46-month follow-up period in patients with STEMI undergoing primary PTCA is the perfusion index, assessed through contrast echocardiography. The incidence of LV remodelling in the group with abnormal myocardial perfusion reached 63% as compared to 11% in patients with normal perfusion, and as many as 42% patients died or needed hospitalisation as a result of heart failure within 5 years [17]. Myocardial perfusion, assessed through angiography according to the MBG or TMPG scale, may be the marker of the real efficacy of the intervention in patients with STEMI undergoing primary PTCA [17, 65, 66]. Evidence is emerging that the MBG index in patients with acute myocardial infarction after primary PTCA correlates with the infarct area assessed enzymatically and is a better predictor of long-term mortality, incidence of adverse cardiovascular events or deterioration of LV function than the Killip class, TIMI scale or EF value [14]. In our study the angiographic index of myocardial perfusion (TMPG) was assessed only in 27% patients. The fact, therefore, that there was no normal perfusion (TMPG score 0–1) in 48% of these patients, despite TIMI 3 flow restoration in IRA, is of limited value. Wita et al. [28] had similar results and found preserved myocardial perfusion (defined as MBG scale grade 2–3) only in 53.3% patients, despite flow restoration in IRA and administration of GP IIb/IIIa receptor blockers in 71.1% persons. In this study the value of the MBG index in predicting the occurrence of LV remodelling was doubtful since MBG scale 2–3 perfusion was noted in patients both with and without adverse LV remodelling [28].

Some reports indicate the good correlation between plasma BNP level and mortality in patients with STEMI. This introduces an additional parameter, independent of the known factors (clinical data, ECG findings, troponin), into the range of popular risk assessment scores [70, 71]. The value of this parameter is concerned both in increased BNP and NT-proBNP levels on admission to hospital [63] and in persistent increased or augmenting NT-proBNP levels over 72 h or within 3–4 weeks of myocardial infarction [58]. The absence of a significant increase in the plasma NT-proBNP level in the present study population during 6 months follow-up could be an indicator of low risk of adverse cardiovascular events in this period.

Study limitations

The limitations of the study are the relatively short duration of follow-up, the small population and the lack of routine coronary angiography during follow-up and angiographic evaluation of microvascular perfusion in all the patients enrolled. Application of new methods of LV function and myocardial perfusion assessment (using contrast echocardiography and tissue Doppler echocardiography) would enable a more reliable evaluation of primary PTCA efficacy to be obtained. Assessment of plasma NT-proBNP levels on the day of discharge could also prove useful with reference to the reports in the literature which emphasise the significance of a second plasma NT-proBNP peak on days 5–7 after STEMI.

Conclusions

1. Successful primary PTCA in patients with STEMI results in significant improvement in the LV systolic function and prevents adverse LV remodelling in a 6-months follow-up.
2. Low baseline NT-proBNP, low CPK_{max} activity and high EF at discharge are powerful independent predictors of EF preservation 6 months after intervention.
3. High baseline NT-proBNP and small LVEDD at discharge are prognostic factors of LV remodelling.

4. A longer delay in reperfusion treatment is associated with a lack of LV systolic function improvement and has no significant impact on the occurence of LV remodelling.

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