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Predictive value of NT-pro BNP after acute myocardial infarction: Relation with acute and chronic infarct size and myocardial function

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ABSTRACT

Aim of the study: We sought to assess the relation of N-terminal brain natriuretic peptide (NT-pro BNP) determined on day 3 after onset of acute myocardial infarction (AMI) symptoms with acute and chronic infarct size and functional parameters assessed by cardiac magnetic resonance (CMR) imaging. Furthermore, we wanted to investigate its predictive value for recovery of myocardial function.
Methods: CMR was performed in 49 consecutive patients within 6 days and in a subgroup 4 ($n=27$) and 12 ($n=22$) months after first acute ST-elevation AMI and successful primary angioplasty. NT-pro BNP was measured in the subacute phase at 66 ± 8 h after onset of symptoms.
Results: Log-transformed NT-pro BNP (lgNT-pro BNP) significantly correlated with infarct size in % of left ventricular myocardial mass ($r=0.59$ to 0.64; $p<0.004$), with ejection fraction (EF) ($r=-0.49$ to -0.55; $p<0.004$) as well as with segmental wall thickening (SWT, mm) ($r=0.41$ to -0.52; $p<0.04$) at any time of assessment. Multiple linear regression analysis revealed baseline EF and lgNT-pro BNP to predict global functional recovery. Patients with NT-pro BNP concentrations <the mean level of 1115 pg/ml significantly improved in EF and SWT (all $p<0.02$) during the study period, whereas patients with NT-pro BNP >1115 pg/ml did not show significant functional recovery (all $p=$NS).
Conclusion: NT-pro BNP on day 3 after admission correlates with acute and chronic infarct size and myocardial function after AMI. Global and regional myocardial function did not recover in patients with higher NT-pro BNP (>1115 pg/ml) during subacute phase of AMI.

1. Introduction

Infarct size is an important prognostic variable with a strong correlation with mortality after acute myocardial infarction (AMI) [1,2]. Left ventricular function is a powerful prognostic indicator too, and is strongly and inversely related to patients' outcome, with rapidly increasing mortality rates at left ventricular ejection fraction (LVEF) <40% [3]. For an optimal management of patients presenting with AMI there is a need for reliable markers for diagnostic evaluation, therapeutic decision-making and estimation of prognosis. There are several methods for the assessment of infarct size and myocardial function in humans including biochemical markers of myocardial damage, and noninvasive imaging techniques, such as echocardiography [4], technetium-99 m sestamibi single photon emission computed tomography (SPECT) [5], thallium-201 SPECT [6] and contrast-enhanced cardiac magnetic resonance imaging (ce-CMR) [7]. Among these imaging methods, the currently preferred technique for infarct size evaluation is ce-CMR with a gadolinium-based contrast agent. It provides high-resolution delineation of infarct size with diagnostic accuracy and good reproducibility with minimal inter- and intraobserver variability [8–10]. It closely correlates with clinical measurements of infarct size *in vivo* [11] and with histological infarct size ($r=0.99$) [8] and, in contrast to other imaging techniques, it allows an exact visualization of even very small subendocardial infarcts [12,13]. The cardiac neurohormone NT-pro BNP is released in response to increased left ventricular wall stretch [14], and, according to several experimental and clinical trials, myocardial ischemia and infarction also trigger its secretion [15–18]. In patients with AMI, plasma NT-pro BNP levels have been shown to reflect the degree of left ventricular (LV) dysfunction; thus, they have prognostic significance and correspond with short- and long-term mortality after acute coronary syndromes [19–21]. Although CMR is highly reliable in detecting infarct size and quantifying LV function, it is an expensive procedure and mostly available only in dedicated centres [11]. By contrast, simple biochemical markers such as NT-pro BNP are cost-

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effective, easy-to-implement and widely available tools. In the present study we analysed whether NT-pro BNP would be a discerning marker for the estimation of infarct size and of LV-function during the subacute phase as well as in longterm follow-up after AMI. Furthermore, we investigated the significance of high NT-pro BNP concentration during the subacute phase of AMI as a marker for impaired functional recovery.

2. Materials and methods

2.1. Patient population

The study population was recruited from consecutive patients admitted to the coronary care unit of the Department of Internal Medicine, Innsbruck University Hospital, Austria, over a 15-month period (October 2006 to December 2007) with the diagnosis of first AMI. Inclusion criteria were a) diagnosis of ST-elevation myocardial infarction (STEMI) according to the redefined ESC/ACC committee criteria [22] as a first cardiac event b) exact determination of time from onset of symptoms until revascularization of the infarct-related artery (pain-to-balloon-time), c) Killip class <2 and no pre-existing condition of heart failure in order to focus on the effect of myocardial infarction itself on the release kinetics of NT-pro BNP. Furthermore, only patients with d) a pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow 0 and a post-procedural TIMI 3 flow and e) a serum creatinine level <114.92 μmol/l and f) without any contraindications for MRI were eligible for this study. The final baseline study population comprised of forty-nine patients (42 males and 7 females, mean age = 56 ± 11.2 years; range 36 to 84 years). A subgroup of patients living close to the University Hospital was followed-up. First follow-up CMR scan was performed on 27 (22 males, 81.5%) of the 49 baseline patients 4 months after AMI (127.84 ± 1.4 days; range 93 to 142 days). Of these, 22 patients (17 males, 77.3%) were followed-up for a period of 12 months (13.2 ± 1.2 months); 5 patients refused additional CMR examination. Baseline characteristics including age, sex, delay in pain-to-balloon time, infarct location and concentration of NT-proBNP as well as CMR assessed parameters including ejection fraction (EF), end-diastolic and end-systolic volume (EDV, ESV), segmental wall thickening (SWT) and infarct sizes in gram and percent of left ventricular myocardial mass (LVMM) differed not significantly between patients with and those without follow-up scan. Infarct related arteries were the left anterior descending artery (LAD) in 22 patients (44.9%), the right coronary artery (RCA) in 20 patients (40.8%) and the left circumflex artery (LCX) was affected in 7 patients (14.3%). 33 (67.3%) patients received GP IIb/IIIa-antagonists. Patients` medication at discharge included aspirin in 49 (100%) patients, clopidogrel in 48 (98%), angiotensin-converting enzyme (ACE) inhibitors in 36 (73.5%), beta-blockers and statins in 46 (93.9%) patients, respectively (Table 1). All patients underwent successful percutaneous coronary intervention (PCI) of the culprit lesion with a median delay of 3 h and 44 min (range 0.5 to 12 h), and 4 patients received thrombolysis therapy before PCI. CMR scans were performed on patients still hospitalized 3.12 ± 1.3 days after AMI and additionally, 4 months (127.84 ± 1.4 days) and 12 months (13.2 ± 1.2 months) after AMI. During the follow-up period of the study no patient died. The study was approved by the local ethics committee and informed consent was obtained from each patient before inclusion in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Biochemical measurements

Blood samples were taken during the subacute phase on the 3 rd day after onset of AMIrelated symptoms. NT-pro BNP was measured quantitatively at an average of 66 ± 8 h (43–84 h) using a sandwich electrochemiluminescence immunoassay (E170, Roche Diagnostics) [23].

Furthermore, blood samples for cardiac troponin T (cTnT) and creatine kinase (CK) were collected according to a standard protocol (at least 3 times during the first 24 h after admission and then daily until normalisation). CK and cTnT concentrations were measured 24 (23 ± 3), 48 (45 ± 7) and 72 (69 ± 6) h after onset of AMI-related symptoms. Furthermore, cumulative release CK and cTnT were estimated by calculation of the cumulative sum and by dividing this value by the number of measuring time points.

Maximum values of both cardiac markers, defined as highest in the concentration time course, were determined from serial samples. CK activity was determined by an enzymatic assay (Roche Diagnostics) and cTnT concentrations were measured by enzyme immunoassays (Roche Diagnostics).

Table 1
Infarct-related arteries and patient`s medication at discharge.

	(n = 49)
Infarct-related arteries	
Left Anterior Descending Artery (LAD)	22 (44.9%)
Right Coronary Artery (RCA)	20 (40.8%)
Left Circumflex Artery (LCX)	7 (14.3%)
Medication at discharge	
Aspirin	49 (100%)
Clopidogrel	48 (98%)
Angiotensin-converting enzyme inhibitors	36 (73.5%)
Beta blocker	46 (93.9%)
Statin	46 (93.3%)

2.3. Cardiac magnetic resonance imaging

We performed CMR within 6 days after AMI during hospital stay and additionally in a subgroup of patients, 4 and 12 months thereafter. Patients were examined with a 1.5 Tesla (T) MR scanner (Magnetom Avanto, Siemens, Erlangen, Germany) providing a total imaging matrix and positioned to the spine array coil and covered by an 8-channel array coil, resulting in a total of 16 array elements for signal collection.

2.3.1. Cine-MR protocol

End-diastolic (EDV) and end-systolic (ESV) as well as ejection fraction (EF) and myocardial mass (MM) were obtained from short axis (11 slices, slice thickness (SL): 8 mm, interslice gap: 2 mm) cine-MR images, acquired using breath-hold, with retrospective ECG-triggered trueFISP (Fast Imaging with Steady-State Precession) bright-blood sequences (Field of View (FoV): 350 × 263 mm, matrix of 320 × 260, voxel size (VS): 2.6 × 1.8 × 8.0 mm, echo time (TE): 1.1 ms, repetition time (TR): 46.8 ms, flip angle: 71°) with generalized autocalibrating partial parallel acquisition (GRAPPA, acceleration factor: 2) reconstruction. An observer blinded to the clinical and biochemical measurements evaluated the cine-MR images semi-automatically by contouring left ventricular endo- and epicardial borders using standard post-processing software (ARGUS, Siemens Erlangen, Germany) and AHA-17 segment model [24] with no evaluation of apical segment 17. By multiplying the wall volume with the specific density of cardiac muscle (1.05 g/cm^3) was maintained left ventricular myocardial mass (MM). Myocardial end-diastolic (ED) to end-systolic (ES) segmental wall thickening (SWT) analysis was performed on the basis of the same endo- and epicardial contours. For each segment, end-diastolic and end-systolic wall thickness (EdWth, EsWth [mm]) as well as segmental wall thickening (SWT [mm]) was assessed and calculated.

2.3.2. Contrast-enhanced CMR protocol

Ten min after injection of a 0.2 mmol/kg body mass gadolinium contrast bolus (Spectris, Medrad, Pittsburgh, PA) [25] into the cubital vein at a flow rate of 5 mL/s by using a commercially available MR injector (Spectris, Medrad, Pittsburgh, PA), late-enhancement (LE) — CMR was acquired by using an ECG-triggered phase-sensitive inversion recovery (PSIR) single-shot balanced steady-state free precession sequence with consecutive slices perpendicular to the short axis with an SL of 8 mm, an interslice gap of 2 mm, a FoV of 400 × 363 mm, a matrix of 256 × 232, a VSof 2.2 × 1.6 × 8.0 mm, aTR of 590 ms, aTEof 1.2 ms, an FA of 45° , and a GRAPPA iPat factor of 2. Planimetry of LE was evaluated quantitatively for each slice and segment using a commercially available software tool (J-Vision vs. 3.3.16, TIANI Medgraph, Brunn am Gebirge, Austria). To define hyperenhancement, a threshold of + 5 SD above the signal intensity of normal myocardium in the opposite non-infarcted myocardial segment was determined [26–28]. By multiplying the hyperenhanced area with slice thickness including the inter-slice gap, the infarct volume [cm^3] was calculated and by multiplying the volume with the specific density of cardiac muscle (1.05 g/cm^3), the infarct mass [g] was assessed. To estimate the percentage of infarcted myocardium, infarct mass was divided by a hundredth of the myocardial mass according to cine-MRI.

2.4. Statistical analysis

For statistical analysis, the statistical software package SPSS 16.0 (SPSS, Chicago, IL) was applied. Kolmogorov-Smirnov test was used to test for normal distribution. NT-proBNP values were log-transformed before statistical analysis because of their skewed distribution. Pearson test was used for calculation of linear correlation for selected variables if they were distributed normally; otherwise Spearman rank correlation coefficients were calculated. The independent samples Student's *t*-test was used to assess any significant difference in the infarct size and functional parameters between two patient groups. The paired samples Student's *t*-test was used to determine statistical significance of functional recovery between baseline and follow-up scans separately for the different groups. Statistical power analyses were performed by calculating the ß-value for two-tailed independent and paired-samples tests. A ß value <0.2 was considered to be adequately powered. Data is expressed as mean ± standard error (SE) if not presented otherwise. All statistical tests were 2-tailed and a p value <0.05 was considered to indicate statistical significance.

Relevant clinical parameters (age, creatinin, delay in time-to-reperfusion, lgNT-pro BNP and maximum concentrations of cTnT and CK) as well as baseline CMR parameters (infarct size in gram and ejection fraction) were included as independent variables in a multiple linear regression analyses to determine independent influences on the recovery of global myocardial function (dependent variable). Parameters were selected stepwise using F-Test, parameters with (p value <0.10) were considered in a final multivariate linear regression model and their corresponding regression coefficients including 95% confidence intervals (95% CI) are presented. The R^2 coefficient was used to describe the proportion of variability in the EF-improvement variable that was explained by the multivariate model.

3. Results

The clinical baseline characteristics of the study population are presented in Table 1. The mean calculated infarct size was 19 ± 2.2 g at baseline scan (BL, $n = 49$) and decreased significantly to 12 ± 2.1 g ($p < 0.007$) after 4 months (4-FU, $n = 27$) and was 11 ± 2.1 g (p = NS) at the 12-month follow-up (12-FU). Mean levels of lgNT-pro BNP were 2.80 pg/ml (range = 1.80 to 3.66 pg/ml) which equates to 1115.14 pg/ml NT-pro BNP (range = 64 to 4627 pg/ml).

3.1. Correlations with CMR-estimated infarct size and LV-function

LgNT-pro BNP values significantly and positively correlated with infarct size in gram (ISg) and percent (IS%) of left ventricular myocardial mass at any time of assessment (Fig. 1): (ISg: $r = 0.52$, $p = 0.0001$ at BL; $r = 0.57$, $p = 0.002$ at 4-FU; $r = 0.46$, $p = 0.02$ at 12-FU); (IS%: $r = 0.60$, $p = 0.0001$ at BL; $r = 0.64$, $p = 0.001$ at 4-FU; $r = 0.59$, $p = 0.004$ at 12-FU). Furthermore, lgNT-pro BNP values were inversely correlated with global (EF) and regional (SWT) myocardial function measured by CMR at any time of assessment (EF: $r = -0.49$, $p = 0.0001$ at BL; $r = -0.55$ $p = 0.004$ at 4-FU; $r = -0.53$, $p = 0.01$ at 12-FU), (SWT: $r = -0.41$ to 0.52, all $p < 0.04$) as well as with SV at BL and at 4-FU ($r = -0.46$ and $r = -0.50$, respectively; $p < 0.008$) but not with ESV, EDV or MM ($p > 0.05$) (Fig. 2).

3.2. Recovery of global and regional function

Average LV-EF was 41.2 ± 2.0% ($n = 27$) at baseline scan and improved significantly up to 46.5 ± 2.0% ($p < 0.001$, $n = 27$) at the follow-up after 4 months and to 47.7 ± 1.7% (p = NS, $n = 22$) after 12 months (Fig. 3).

Segmental wall thickening [mm] (SWT) improved significantly from baseline (3.62 ± 0.1 mm) to 4-FU (4.88 ± 0.3 mm, $p = 0.02$) and remained unchanged thereafter (4.64 ± 0.6, p = NS).

To determine the predictive power of NT-pro BNP for recovery of global and regional left ventricular function, patients were divided into two groups, based on their mean value of lgNT-pro BNP measured on day 3 after onset of AMI-related symptoms: group 1 with lgNTpro BNP > 2.80 pg/ml (= 1115 pg/ml) and group 2 with NT-pro BNP < 2.80 pg/ml (= 1115 pg/ml). There were significant differences in baseline EF ($p = 0.0001$), in baseline SV ($p = 0.003$), in baseline SWT [mm] ($p = 0.001$), as well as baseline infarct size in gram ($p = 0.001$) and infarct size in % of LVMM ($p = 0.0001$) between the two groups. Furthermore, at 4-FU there were significant scan differences in EF ($p = 0.001$), in SV ($p = 0.007$), in SWT [mm] ($p = 0.01$) and in infarct size in gram ($p = 0.0001$) as well as in infarct size in % of LVMM ($p = 0.002$) between the two groups. At 12-FU

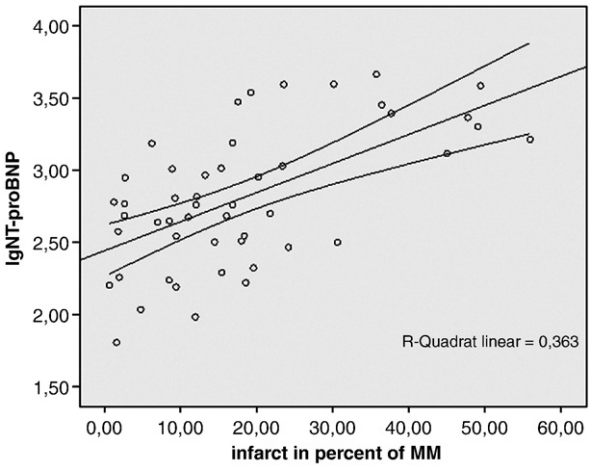

Fig. 1. Linear correlation between lgNT-pro BNP and infarct size in percent of left ventricle myocardial mass (LVMM) during the subacute phase of AMI. There was a close correlation between lgNT-pro BNP and infarct size in % of LVMM ($r = 0.60$, $p < 0.0001$) at baseline scan ($n = 49$).

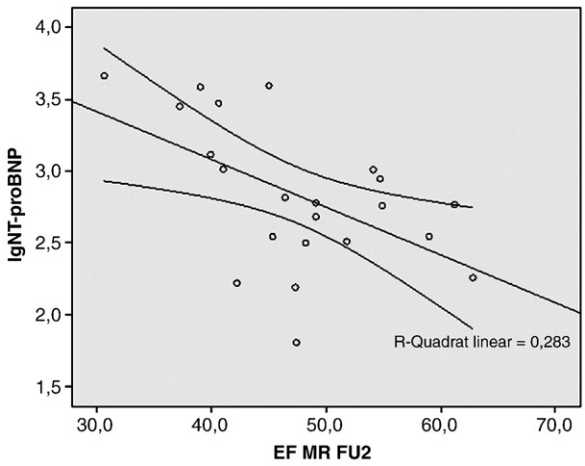

Fig. 2. Linear correlation between lgNT-pro BNP and 12-FU ejection fraction (EF). There was a moderate correlation between lgNT-proBNP and EF (%) quantified 12 months after AMI ($n = 22$). ($r = -0.53$, $p < 0.01$).

scan differences between the two groups were more pronounced in EF ($p = 0.0001$), in IS gram ($p = 0.04$) and IS in % of LVMM ($p = 0.01$). (Table 2) Group 2 (<1115 pg/ml) showed significant improvement of their global and regional left ventricular function over 4 months (EF: $p < 0.004$, SWT [mm]: $p < 0.02$) but did not show any significant improvements in EF and SWT beyond the fourth month after AMI (p = NS). ESV in this group decreased significantly from BL to 4-FU (68 ± 3 to 58 ± 4 ml, $p < 0.02$. Furthermore, infarct size in grams of this group significantly decreased from baseline to the first follow-up scan (13 ± 2 to 9 ± 2 g, $p < 0.01$), whereas differences between the follow-ups at 4 and 12 months were no longer significant (p = NS) (Table 3). In contrast, group 1 (>1115 pg/ml) showed neither significant improvement of EF and SWT nor reduction in ESV (p = NS). Nevertheless, decrease of infarct size in gram was significant over a period of 12 months (35 ± 3 g at BL to 21 ± 4 g at 12-FU, $p < 0.001$). As shown is Table 4, baseline EF and lgNT-proBNP have significant influence on the recovery of global myocardial function. The *R* squared of this model was 0.260, indicating that the model explained 26.0% of the variance in EF-improvement.

3.3. Statistical power analysis

Power analyses on the results obtained by two-tailed independent student-*t* test between the two groups revealed a ß < 0.2 for all statistical significant results (range 83.3% to 100% power). For paired student-*t* test performed on changes of EF, SV, SWT and infarct size in gram and % of LVMM between the different timepoints of assessment

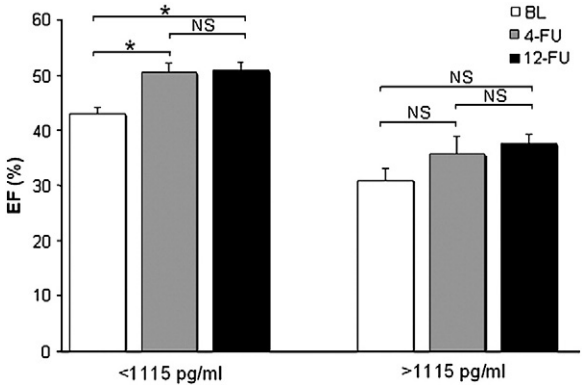

Fig. 3. Patients with NT-pro BNP concentrations <1115 pg/ml measured on day 3 after acute myocardial infarction related symptom onset showed significant (* = $p < 0.004$) improvement of ejection fraction (EF%) during 4 and 12 months, respectively. Patients with higher NT-pro BNP concentrations (>1115 pg/ml) did not show significant recovery of global myocardial function (p = not significant, NS).

Table 2
Clinical characteristics of the study population.

	Baseline cohort $n=49$ (100%)
Study variable	
Mean age	56 ± 11.2
Female *n*	7 (14.3%)
STEMI	49 (100%)
Pain-to-balloon-time, min	224.18
Delay AMI onset to CMR, days	3.12 ± 1.3
Prehospital fibrinolysis	4 (8.2%)
p-PTCA	45 (91.8%)
GP IIb/IIIa antagonists	33 (67.3%)
Infarct size (gram)	19 ± 2.2
Infarct size (% of LV-MM)	17.9 ± 14.21
EF, (%)	39.44 ± 9.63
Delay to NT-pro BNP sampling (hours)	66 ± 8
Cardiovascular risk factors	
Hypertension	25 (67.6%)
Current smoking	16 (43.2%)
Hypercholesterolemia	29 (78.4%)
Diabetes mellitus	4 (10.8%)
Creatinine (μmol/l)	80.444 ± 19.448
Positive family history	3 (8.1%)

either in the higher and lower NT-pro BNP group, ß values were <0.1 (range 91.4% to 96.5% power).

3.4. Correlation with biomarkers of myocardial necrosis

Subacute lgNT-pro BNP concentrations were significantly and positively correlated with CK and cTnT concentrations as measured 24, 48 and 72 h after AMI related symptom onset as well as with maximum and cumulative release CK and cTnT concentrations ($r=0.47$ to 0.63, all $p<0.001$). Single values (24, 48 and 72 h after symptom onset) of CK and cTnT values significantly correlated with infarct size in gram (ISg) and percent (IS%) of left ventricular myocardial mass at any time of assessment (IS: $r=0.59$ to 0.91, all $p<0.001$), with EF ($r=-0.47$ to -0.77, all $p<0.005$), and with ESV at any time of assessment ($r=0.40$ to 0.64, all $p<0.04$). When compared to single values of CK and cTnT, lgNT-pro BNP showed similar correlations with infarct size and parameters of left ventricular myocardial function. However, maximum and cumulative release CK and cTnT concentrations showed the closest correlations with infarct size and EF as assessed early, on midterm as well as on long-term CMR follow-up scan (IS: $r=0.64$ to 091, all $p<0.0001$), (EF: $r=-0.53$ to -0.77, all $p<0.001$).

Table 3
Functional parameters and infarct size of patients with NT-pro BNP on day 3 after admission above and below 1115 pg/ml and statistical significances.

	<1115 pg/ml	>1115 pg/ml	*p*
Baseline	$n=35$	$n=14$	
EF	42.89 ± 1.3	30.81 ± 2.3	<0.0001
SV	55.40 ± 2.2	39.84 ± 4.0	<0.003
SWT	3.9 ± 0.18	2.74 ± 0.2	<0.001
IS	13.07 ± 1.6	33.82 ± 4.7	<0.001
IS	11.76 ± 1.2	33.55 ± 4.0	<0.0001
4-FU	$n=19$	$n=8$	
EF	50.46 ± 1.8	35.82 ± 2.9	<0.0001
SV	57.99 ± 3.2	40.45 ± 4.4	<0.007
SWT	5.44 ± 0.4	3.29 ± 0.5	<0.01
IS	8.38 ± 1.8	26.22 ± 2.7	<0.0001
IS	9.35 ± 1.8	30.67 ± 4.1	<0.002
12-FU	$n=16$	$n=6$	
EF	50.85 ± 1.6	37.46 ± 1.8	<0.0001
SV	54.15 ± 3.1	44.28 ± 4.6	NS
SWT	5.09 ± 0.7	3.31 ± 0.4	NS
IS	8.47 ± 1.9	21.62 ± 4.4	<0.03
IS	9.23 ± 1.7	26.84 ± 4.7	<0.01

Abbreviations: EF, ejection fraction; SV, stroke volume; SWT, segmental wall thickening; EdWt, end-diastolic wall thickness; IS, infarct size; 4-FU, 4-month follow-up; 12-FU, 12 month follow-up.

Table 4
Results of multiple regression analyses with EF-Recovery as outcome parameter.

Determinants of EF-recovery	*p*	Standardized ß-coefficient	Lower limit 95% CI	Upper limit 95% CI
Baseline EF	0.01	−0.573	−0.70	−0.10
lgNT-pro BNP	0.09	−0.351	−12.24	1.12

R^2 of the entire model = 0.260.

4. Discussion

The main findings of the present study are the significant correlation of NT-pro BNP measured on day 3 after admission with acute and chronic infarct size, EF and SWT after AMI assessed by CMR as well as with biomarkers of myocardial necrosis. Furthermore, our results highlight the potential of NT-pro BNP concentration (>1115 pg/ml on third day after AMI) to identify patients with no significant recovery of global and regional myocardial function over a period of up to 12 months. Moreover, when considering age, delay in time-to reperfusion, baseline infarct size and EF, creatinin, NT-pro BNP as well as maximum CK and cTnT in a multiple linear regression analysis, baseline EF and NT-pro BNP were significantly related to the mid-term recovery of global myocardial function.

There is limited data about brain natriuretic peptide (BNP) and NT-pro BNP and their association with the extent of myocardial infarct size detected by CMR. In particular, data on the relation of early NT-pro BNP concentration with CMR-assessed mid- and long-term left ventricular function are lacking. Although correlations of BNP with infarct size determined by thallium-201 SPECT [6], technetium-99 m sestamibi SPECT [5], cardiac enzymes [29,30] and contrast-enhanced magnetic resonance imaging (CE-MRI) [30] have been reported previously, few studies have focused on the correlations of NT-proBNP with infarct size. Some recent studies have suggested that NT-proBNP may be superior to BNP in identifying and evaluating cardiac dysfunction [31,32] and therefore its correlation with infarct size and LV function after AMI is of great clinical relevance. Ndrepepa et al. reported a correlation of NT-proBNP measured on admission in patients with AMI and scintigraphic infarct size [33]. Several studies reported on the role of BNP, and that of NT-pro BNP as prognosis markers for mortality after AMI [31,34] and their predictive value according to their relation with EF and LV remodeling [32,35]. Recently, Cochet et al. found correlations between NT-proBNP concentrations on day 3 after AMI and LVEF and infarct size derived from the delayed ce-MR images [36], but they measured NT-pro BNP in a heterogeneous cohort of patients with the whole clinical spectrum of acute coronary syndromes and without long-term monitoring. Some clinical trials suggest that the release kinetics of cardiac markers, especially NT-pro BNP, in patients with STEMI differ from those in non-STEMI-ACS [34]. In agreement with the results of Steen et al. we could confirm in a homogeneous and even larger study population of STEMI patients that NT-pro BNP concentrations during the subacute phase of AMI closely correlate with infarct size calculated in grams and % of LVMM [37]. Steen et al. measured NT-pro BNP not earlier than the fourth day after AMI, and it is likely that the longer the delay from AMI to blood sampling, the more complex is the relation between natriuretic peptide and infarct size due to confounding factors, such as therapeutic reperfusion, drug therapy, and subduing of ischemia. Nilsson et al. demonstrated CMR-assessed LV dilatation during one year in patients with elevated plasma levels early after AMI but they did not report significant correlation of NT-

pro BNP with LVEF and did not investigate segmental ventricular function [32]. In agreement to Ingkanisorn et al. as well as to Choi et al. we found an approximately 30% decrease in infarct size from baseline to first follow-up scan 4 months after AMI, because the absolute infarct size changes as infarcts involute over time [38,39]. NT-pro BNP measured on day 3 after AMI correlated with follow-up infarct sizes in the same performance as with the extent of infarct at baseline scan and hence affirmed its predictive power regarding the assessment of acute and chronic infarct size. CK and cTnT concentrations also closely correlated with CMR estimates of infarct size and global myocardial function at any time of assessment In contrast, biomarkers of myocardial damage correlated exclusively with baseline regional myocardial function but not with SWT as estimated at follow-up scans. However, maximum and cumulative release concentrations of CK and cTnT correlated closest with infarct size and EF at any time of assessment, but they make serial blood sampling necessary, which is not always feasible in daily clinical practice.

Increased wall stress is known to be both a major force driving LV remodeling [35,40] and a cause of NT-pro BNP release [14].Recent studies suggest that BNP may be a high-risk marker for remodeling before chamber dilatation actually occurs [23,41]. Drugs that provide the most important antiremodeling effects appear to be angiotensin-converting enzyme (ACE) inhibitors [42]. Our study population was treated according to current guidelines to prevent remodeling as much as possible. We found no functional recovery in patients with a relatively high absolute concentration of NT-pro BNP during the subacute phase of AMI.

Moreover, the mulitvariate linear regression analysis revealed that NT-pro BNP among baseline EF is a valuable predictor of global myocardial recovery. Baseline EF in an univariate model revealed a R^2 of 0.16, whereas the multvariate regression model including both baseline EF and lgNT-proBNP explain 26.0% of the variance in EF-improvement.

To the best of our knowledge this is the first CMR study to demonstrate the relation of NT-pro BNP with acute and chronic infarct size and both, global and regional myocardial function after STEMI. In conclusion, a single analysis of NT-pro BNP measured in a STEMI patient on day 3 after admission may be a useful tool in the estimation of early and late infarct size and myocardial function as well as a useful predictor of functional recovery after AMI. Our study adds to the growing body of evidence which suggests that NT-pro BNP measured in the subacute phase of AMI is useful for estimating infarct size and LVEF. In addition, high NT-pro BNP appears to identify patients in whom functional recovery after AMI does not occur.

The highly selected and limited number of study participants, mainly at follow-up scans calls for caution in making conclusions. The study patients had a pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow 0 and a post-procedural TIMI 3 flow and whether the results of this study can be extrapolated to patients with different pre- and postprocedural TIMI flows is unclear. Furthermore, the pathophysiologic mechanisms underlying the independent relationship of NT-pro BNP with global functional recovery remains to be elucidated. Since baseline EF and lgNT-pro BNP showed a mild correlation and were used as determinants in the multivariate regression analysis of global functional recovery, regression coefficients have to be interpreted with caution.

5. Conflicts of interest

None.

Acknowledgements

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [43].

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