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Michael Weber, Christian Kleine, Eva Keil, Matthias Rau, Alexander Berkowitsch, Albrecht Elsaesser, Veselin Mitrovic, Christian Hamm

Kerckhoff Heart Centre
Departement of Cardiology
Bad Nauheim, Germany

TIMELY KINETICS OF N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE (NT-PROBNP) RELEASE IN ACUTE CORONARY SYNDROMES

SUMMARY

It has been found recently that BNP and NT-proBNP provide independent prognostic information in patients with acute coronary syndromes (ACS). However, little data are available on the time course of NT-proBNP levels in relation to onset of symptoms.

We included 765 patients (236 females, aged 64±11 years) with an ACS (STEMI 42%, NSTEMI 41%, UAP 17%) who were referred for coronary angiography. NT-proBNP was assessed on admission and the next day. NT-proBNP values were related to the time duration from the onset of symptoms until blood drawing with lowest values within 3 hours and highest values 24-36 hours after the onset of symptoms (147 (64-436) pg/ml and 1099 (293-3795) pg/ml respectively, p<0.001). Highest values for NT-proBNP on admission were found in patients with NSTEMI compared to patients with STEMI and UAP (912 (310-2258) pg/ml) vs. 262 (85-1282) pg/ml) vs. 182 (74-410) pg/ml; p<0.001), but no difference was found between STEMI and NSTEMI the day after admission (1325 (532-2974) pg/ml vs. 1169 (555-3413) pg/ml; p=0.676). In contrast, NT-proBNP values remained unchanged in UAP (182 (74-410) pg/ml) vs.171 (53-474) pg/ml).

The time interval from the onset of symptoms to first blood collection is an important determinant for NT-proBNP values on admission in patients with an ACS and needs to be considered in clinical practice.

Key words: **N-terminal pro B-type natriuretic peptide, NT-proBNP, Acute coronary syndromes, Myocardial infarction**

Background

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are synthesised and secreted from the myocardium in response to ventricular wall stress (1,2). It is well-known that both neurohormones are elevated in patients with congestive heart failure related to disease severity and that they provide independent diagnostic and prognostic information (3-6). Recently, there has been increasing evidence that myocardial ischemia is also a stimulus for the release of BNP and NT-proBNP (7,8). The underlying pathomechanism is not fully understood, but a direct release of BNP from ischemic cardiomyocytes in addition to ischemia-induced increase in ventricular wall stress is discussed and, moreover, there is evidence suggesting a protective role of BNP on the myocardium (9-12).

Consequently, both BNP and NT-proBNP have been found to be elevated in acute coronary syndromes (ACS) with additional prognostic value apart from established cardiac markers, especially troponins (13,14). Data on the diagnostic role of BNP and NT-proBNP in ACS patients are derived mainly from multicenter trials in which BNP and NT-

Corresponding author • Tel. +40 60-32-99-60 / Fax: +49 60-32-99-62-313 • E-mail address: M.Weber@kerckhoff-klinik.de

proBNP have only been assessed as a single measurement at varying time points after the onset of symptoms. Thus, the optimal timing of BNP and NT-proBNP assessment for risk stratification is unclear and studies providing data from serial testing have been demanded (15). So far, data on the prognostic value of serial BNP or NT-proBNP testing have been sparse. Heeschen et al. could demonstrate in a sub-study of the PRISM trial that NT-proBNP assessment at 78 hours is of superior predictive value compared to a single measurement at baseline (16). In contrast, no additional predictive value was found in a study by Jernberg et al. (17) who examined NT-proBNP values on admission and 6 hours thereafter in patients with an ACS. However, in none of these studies, the relation of BNP or NT-proBNP with duration from the onset of symptoms until blood drawing has been analysed. Therefore, we performed a prospective study including patients presenting with the complete spectrum of ACS, ranging from unstable angina pectoris Braunwald class IIIB (UAP) to non-ST-elevation myocardial (NSTEMI) and ST-elevation myocardial infarction (STEMI) with the aim to evaluate the impact of the time interval from the onset of symptoms on NT-proBNP values.

METHODS

Patients and design

In this study, 765 consecutive patients were included from April 2003 till October 2004. All patients were referred for early coronary angiography or primary PCI because of an ACS with an episode of chest pain within the last 48 hours. First, blood drawing was performed on admission directly before angiography and revascularisation, and the second sample was collected the following day (18.9 ± 6.2 hours after admission). STEMI and NSTEMI were defined according to the recommendations of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (18). Myocardial infarction was diagnosed, if cardiac markers, e.g. troponin or CK MB were elevated above the defined cut-off level. For the differentiation between STEMI and NSTEMI commonly used ECG-criteria as defined in the current guidelines were applied. Unstable angina pectoris (UAP) has been diagnosed according to Braunwald class IIIB (19). Patients were either admitted directly by the emergency medical system or were transferred from community hospitals. Pre-treatment with clopidogrel and GP IIb/IIIa inhibitor was left to the discretion of the treating physicians or the emergency staff. Medical history was assessed as the patients reported it or if available from the medical records. The time point of the onset of symptoms was determined as the most severe episode of the chest pain. If there were uncertainties about the time of the index event and patients were not able to determine the onset of pain ± 1 hour, these patients were not considered for this study. A 12 lead electrocardiogram was written on admission and all patients underwent a brief physical examination prior to angiography. Coronary angiography was performed immediately in all patients and a revascularization therapy was performed at the discretion of the interventional cardiologist if appropriate. All patients gave written informed consent prior to inclusion into the study.

Echocardiography

Transthoracic echocardiography was performed with an Agilent Sonos 1.75 – 3.5 Mhz scanner (Phillips Medical Ultrasound) with the use of harmonic imaging within 24 hours after angiography and PCI. All examinations were done by an experienced echocardiographer, blinded to clinical results and to NT-proBNP measurements. Left ventricular diameters were assessed by M-mode in the left parasternal view. Ejection fraction was visually assessed.

Laboratory measurements

Prior to angiography, venous blood was taken from all patients (first sample) and the following day (second sample) from an antecubital vein in gel-filled tubes. The specimens were centrifuged within one hour and serum was frozen at –80° until analysis. NT-proBNP was measured by an electrochemiluminescence-immunoassay (Elecsys proBNP, Roche Diagnostics. Mannheim, Germany). Cardiac troponin T (TnT), creatine kinase activity (CK MB) and myoglobin were measured by an electrochemiluminescence-immunoassay (third generation for cTnT) on an Elecsys 2010 analyzer (Roche Diagnostics. Mannheim, Germany).

Coronary angiography

Invasive diagnostics was performed in all patients by the common technique and percutaneous intervention (PCI) or bypass surgery (CABG) was performed if indicated. Concomitant medication was left to the discretion of the angiographer, but all angiographers were encouraged to treat the patients according to the current guidelines. TIMI flow was graded as described before, with grades 0, 1, 2, and 3 estimated by experienced interventional cardiologists blinded to NT-proBNP results (20).

Statistics

Values for NT-proBNP are given as median and interquartile range, all other variables as mean and standard deviation. For group wise comparisons of NT-proBNP values Mann-Whitney test (2-groups) and the Kruskal-Wallis test (n-groups) were used, for pair wise multiple comparisons of NT-proBNP the Dunnett´s T3 test has been applied. For the analysis of the baseline characteristics of the patients, the t-test (2-groups) or ANOVA (n-groups) were used for continuous variables and the CHI^2 test was used for categorical variables. For the correlation of NT-proBNP with the other cardiac markers, ejection fraction and age, the Spearman correlation coefficient was calculated. Linear multiple regression analysis was performed to evaluate the impact of the variables such as age, gender, body mass index, ejection fraction, history of CAD, symptomatic status, blood pressure on admission, heart rate on admission, angiographic findings, ejection fraction, cardiac troponin T, time duration from the onset of symptoms till blood sampling on logarithmically transformed NT-proBNP. For all statistical analyses, the statistical software SPSS 10.0 for windows was used.

RESULTS

Baseline characteristics

In this study, 765 patients (236 females, aged 64 ± 11 years) were included. According to the abovementioned definitions, STEMI was diagnosed in 323 patients (42%), NSTEMI in 315 patients (41%) and UAP in 127 patients (17%). Hypertension was present in 512 patients (67%), hyperlipidemia in 327 patients (43%), diabetes in 171 patients (22%), 235 patients (31%) were current smokers and 111 patients (15%) reported a family history of coronary artery disease (CAD). A history of CAD was present in 187 patients (24%) of whom 107 patients (14%) had a previous myocardial infarction, 90 patients (12%) had been treated with an interventional coronary revascularisation (PCI) previously and 59 patients (8%) had undergone bypass surgery (CABG). A relevant coronary artery stenosis (?70%) of at least one vessel was diagnosed at angiography in 642 patients (84%). The culprit lesion was located in the left main stem in 21 patients (3%), left anterior descendens in 252 patients (33%), ramus circumflexus in 139 patients (18%), right coronary artery in 204 patients (27%) and a vein graft in 26 patients (3%). Revascularisation therapy was performed in 617 patients – PCI in 580 (76%) and CABG in 37 (5%) patients. A hundred and forty-eight patients (19%) were treated conservatively. Door-to-balloon time of patients who underwent PCI was 151±34 (median 49) minutes in patients with UAP, 125±13 (median 57) minutes in patients with NSTEMI and 34±2 (median 27) minutes in patients with STEMI.

There was no difference in gender distribution between different subgroups.

Patients with NSTEMI were older than patients with STEMI and UAP. A history of CAD was more frequently present in patients with NSTEMI and UAP than in patients with STEMI. Serum creatinine in the entire study group was at average 0.95±0.36 mg/dl (median 0.87 mg/dl, maximum 3.32 mg/dl) and did not differ among study groups. Systolic blood pressure on admission and left ventricular ejection fraction were lower in patients with STEMI than in patients with NSTEMI andUAP, but no differences of heart rates, body mass index and symptomatic status existed between the various groups. In patients with STEMI and NSTEMI, a relevant coronary artery lesion at angiography was found more often than in patients with UAP and an occluded artery with TIMI 0 or I flow at angiography was more frequently found in patients with STEMI than in patients with NSTEMI and was least frequently seen in patients with UAP. There was no difference between different groups with respect to the procedural result as assessed by the TIMI flow. The detailed baseline characteristics of the patients are shown in *Table 1*.

NT-proBNP on admission

Duration from the onset of symptoms until admission and first blood drawing was shortest in the group of patients with STEMI and was longer in patients with NSTEMI and UAP. Patients were divided into groups according to duration from the onset of symptoms until blood drawing on admission (0-3 h; 3-6 h; 6-12 h; 12-24 h; 24-48 h). NT-proBNP values were lowest in the group of patients who were admitted within 3 hours after the onset of symptoms, and values were increasing, with highest values in the group of patients who were admitted 24-48 hours after the onset of symptoms.

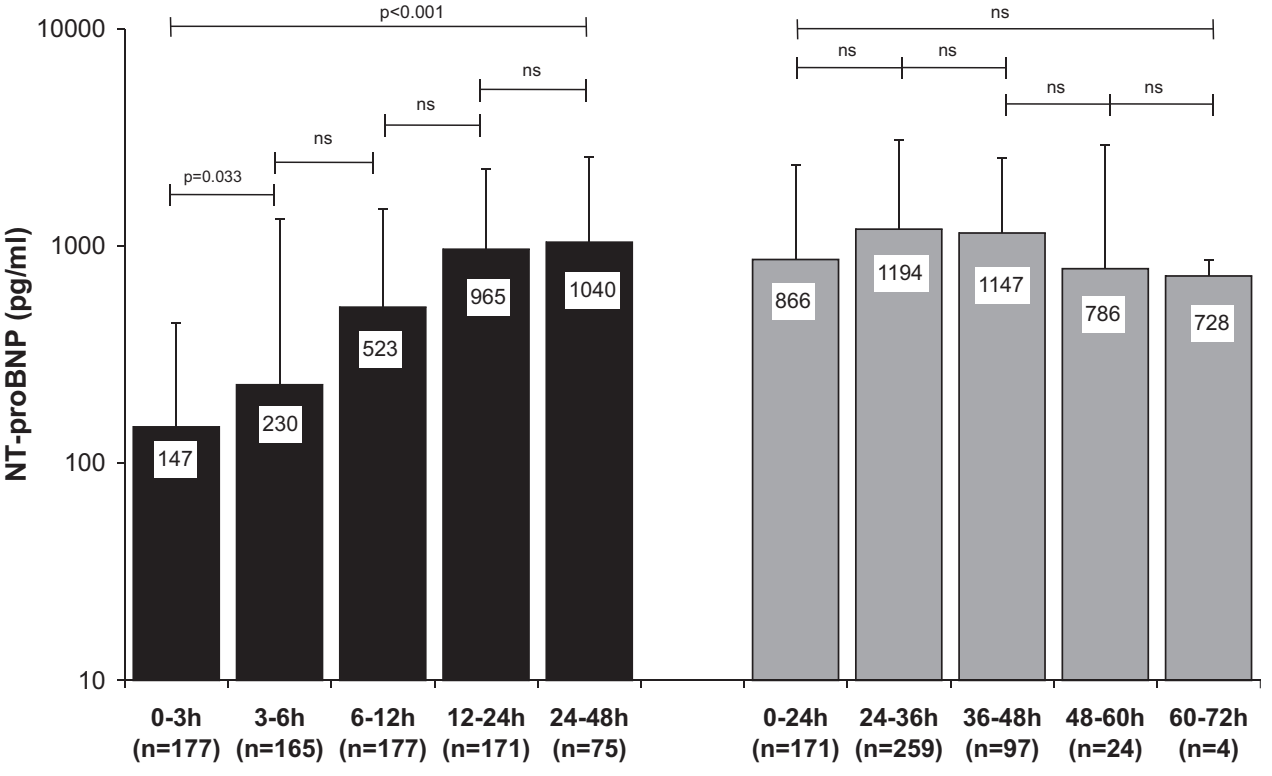
There was a positive and significant correlation between NT-proBNP values and the time from the onset of symptoms to first blood drawing (Spearman Rho = 0.391, $p<0.01$) *(Figure 1 and Figure 2)*.

Other clinical factors associated with higher NT-proBNP values on admission were female gender, age above 65 years (median), the absence of ST-elevation in the ECG, elevated troponin T, a left ventricular ejection fraction below 45%, a history of coronary artery disease, a blood pressure below 100

Table 1.
Baseline data for the entire study group and for the subgroups of patients with unstable angina pectoris (UAP), non-ST-elevation myocardial infarction and ST-elevation myocardial infarction. Values are expressed as mean ± standard deviation (median) or as median (interquartile range) for NT-proBNP and cTnT. Values on admission were derived from all 765 patietns, whereas values at day 1 were derived from 555 patients. P-values refer to global testing with the use of either Kruskal-Wallis-test, ANOVA-test or CHI-square test.

	all patients	UAP	NSTEMI	STEMI	p
n	765	127	315	323	
Age (years)	64 ± 12 (65)	62 ± 11 (63)	66 ± 12 (67)	64 ± 13 (64)	0.005
Gender (female/male, % female)	236/529 (31%)	36/91 (28%)	99/216 (31%)	101/222 (31%)	0.808
BMI (kg/m2)	27.5 ± 4.2 (27.2)	27.8 ± 3.7 (27.8)	27.8 ± 4.4 (27.4)	27.1 ± 4.1 (26.6)	0.077
History of CAD (n/%)	187 (24%)	36 (28%)	87 (27%)	64 (20%)	0.038
Persistend AP at addmission (n/%)	93 (12%)	14 (11%)	30 (10%)	49 (15%)	0.095
Systolic blood pressure (mm Hg)	139 ± 27 (140)	146 ± 26 (144)	141 ± 29 (140)	134 ± 26 (135)	< 0.001
Heart rate (beats/min)	78 ± 16 (77)	77 ± 13 (77)	79 ± 16 (78)	78 ± 17 (76)	0.529
Creatinine (mg/dl)	0.95 ± 0.36 (0.87)	0.92 ± 0.37 (0.83)	0.98 ± 0.34 (0.90)	0.95 ± 0.38 (0.87)	0.452
Ejection fraction (%)					
<35%	107 (14%)	5 (4%)	38 (12%)	65 (20%)	
35-50%	227 (30%)	13 (10%)	92 (29%)	123 (38%)	< 0.001
>50%	430 (56%)	109 (86%)	185 (59%)	136 (42%)	
Angiographic findings					
0 VD (n/%)	123 (16%)	61 (48%)	35 (11%)	27 (8%)	<0.001
1 VD (n/%)	286 (37%)	23 (18%)	117 (37%)	146 (45%)	
2 VD (n/%)	206 (27%)	25 (20%)	88 (28%)	93 (29%)	
3 VD (n/%)	150 (20%)	18 (14%)	75 (24%)	57 (18%)	
TIMI flow at baseline					
0/I (n/%)	296 (47%)	10 (13%)	105 (41%)	181 (62%)	< 0.001
II/III (n/%)	333 (53%)	69 (87%)	154 (59%)	110 (38%)	
TIMI flow post procedure					
0/I (n/%)	24 (4%)	3 (4%)	11 (4%)	10 (3%)	0.753
II/III (n/%)	593 (96%)	73 (96%)	243 (96%)	277 (97%)	
Time span from onset of symptoms to blood drawing at baseline (h)	10.4 ± 9.3 (6.9)	10.1 ± 9.1 (6.6)	14.2 ± 9.8 (12.3)	6.8 ± 7.1 (4.2)	< 0.001
Time span to blood drawing at day 1 (h)	29.3 ± 10.1 (27.5)	28.1 ± 10.1 (25.5)	32.2 ± 10.6 (32)	27.0 ± 8.8 (26.0)	< 0.001
NT-proBNP at baseline (pg/ml)	451 (127-1487)	182 (74-410)	912 (310-2258)	262 (85-1282)	< 0.001
NT-proBNP at day 1 (pg/ml)	1048 (377-2858)	171 (53-474)	1169 (555-3413)	1325 (532-2974)	< 0.001
Delta NT-proBNP (pg/ml)	351 (16-1163)	19 (-12-129)	318 (4-1122)	666 (172-1764)	< 0.001
cTroponin T at baseline (ng/ml)	0.18 (0.01-0.67)	0.01 (0.01-0.01)	0.35 (0.15-0.83)	0.17 (0.01-0.96)	0.01
cTroponin T at day 1 (ng/ml)	0.92 (0.16-2.69)	0.01 (0.01-0.01)	0.65 (0.27-1.67)	2.19 (0.91-4.08)	< 0.001

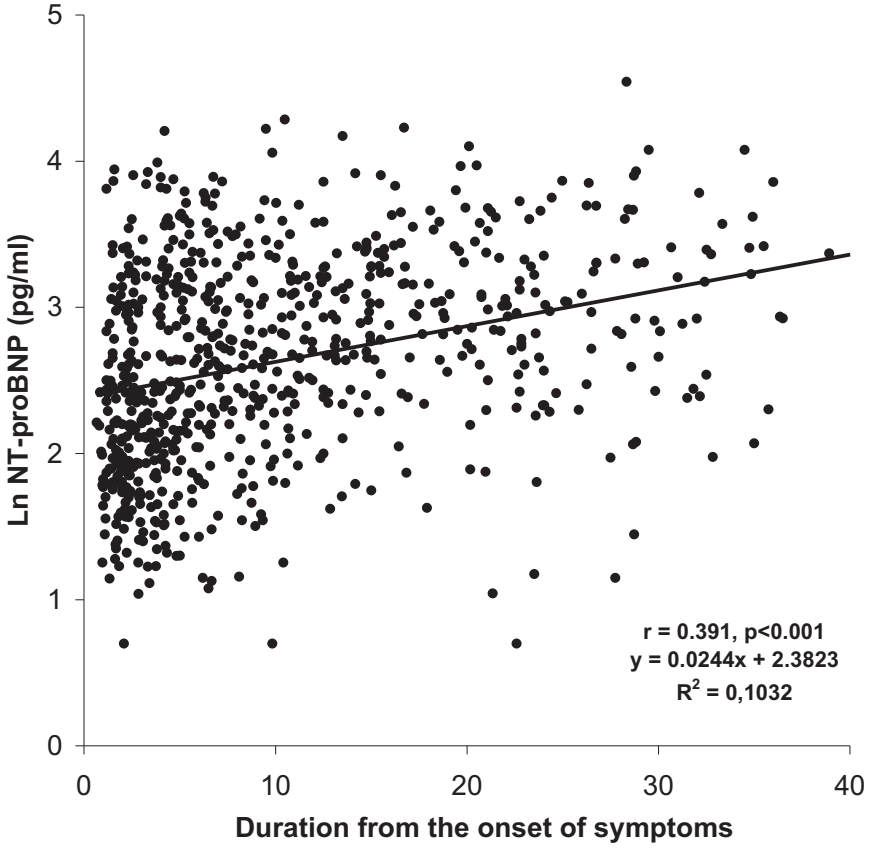
Figure 1. Relation of NT-proBNP to the time interval from the onset of symptoms until blood drawing. Black bars NT-proBNP on admission, grey bars NT-proBNP at day 1. Values are expressed as median and the 75th percentile.



mm Hg on admission and a heart rate above 100 bpm on admission *(Table 2)*.

However, in a multivariate analysis, only duration from the onset of symptoms, cTnT on

Figure 2. Correlation of logarithmically transformed NT-proBNP on admission with duration from the onset of symptoms



admission, persistent angina pectoris on admission, gender, age, ejection fraction and heart rate remained independent determinates for logarithmically transformed NT-proBNP values on admission with age and duration from the onset of symptoms as the strongest determinants *(Table 3)*.

Values for NT-proBNP on admission in patients with NSTEMI were higher than the values of

Table 2. Univariate analysis of impact of the dichotomised clinical variables on NT-proBNP values assessed on admission and at day 1. Values are expressed as median (interquartile range)

	NT-proBNP (pg/ml) on admission	p-value
Gender male vs. female	318 (93-1098) vs. 890 (230-2422	<0.001
Age =65 vs. > 65 years	247 (65-842) vs. 854 (236-2389)	<0.001
No ST-elevation vs. ST-elevation	608 (212-1722) vs. 262 (85-1282)	<0.001
Troponin positiv vs. negativ	687 (189-1901) vs. 157 (65-404)	<0.001
Ejection fraction >45% vs. =45%	267 (87-844) vs. 818 (218-2231)	<0.001
Blood pressure =100 vs. >100 mm Hg	1141 (183-3791) vs. 430 (121-1366)	<0.001
Heart rate =100 vs. >100 bpm	428 (125-1383) vs. 1261 (385-3850)	<0.001
History of CAD yes vs. No	691 (200-1881) vs. 388 (110-1367)	0.001
TIMI flow after PCI 0/1 vs. II/III	957 (241-3584) vs. 452 (129-1377)	0.104
Persistent Angina pectoris yes vs. No	397 (95-1351) vs. 462 (139-1517)	0.195
Cardiogenic shock yes vs. No	889 (158-3463) vs. 453 (129-1482)	0.207
TIMI flow on admission 0/1 vs. II/III	486 (112-1593) vs. 446 (131-1372)	0.743
	NT-proBNP (pg/ml) at day 1	p-value
Gender male vs. female	801 (287-1987) vs. 2225 (812-1098)	<0.001
Age =65 vs. > 65 years	660 (211-1378) vs. 2033 (736-4707)	<0.001
Ejection fraction >45% vs. =45%	595 (212-1286) vs. 2209 (880-4486)	<0.001
Blood pressure =100 vs. >100 mm Hg	2180 (991-6268) vs. 987 (336-2732)	<0.001
Troponin positiv vs. negativ	1342 (603-3158) vs. 166 (51-464)	<0.001
Heart rate =100 vs. >100 bpm	997 (355-2545) vs. 4077 (965-8271)	<0.001
TIMI flow at admission 0/1 vs. II/III	1418 (726-2955) vs. 863 (289-2520)	<0.001
Cardiogenic shock yes vs. No	3359 (2054-5225) vs. 1027 (367-2828)	0.003
No ST-elevation vs. ST-elevation	873 (302-2516) vs. 1325 (532-2974)	0.005
History of CAD yes vs. No	1165 (453-3714) vs. 976 (341-2802)	0.065
TIMI flow after PCI 0/1 vs. II/III	1506 (534-2852) vs. 1123 (481-2848)	0.547
Persistent Angina pectoris yes vs. No	1169 (458-3363) vs. 1028 (139-1517)	0.277

patients with STEMI and UAP *(Table 1, Figure 3)*.

In 61 (48%) of patients with UAP relevant coronary artery disease was ruled out. Those patients had lower NT-proBNP values as those patients with relevant CAD (116 (35-318) pg/ml vs. 259 (103-503) pg/ml; p=0.003). Comparing patients with NSTEMI and STEMI and stratifying them according to the time delay from the onset of symptoms, we found

Table 3. Multivariate linear regression analysis for the dependent variable NT-proBNP, logarithmically transformed, assessed on admission and at day 1.

Dependent Variable logarithmically transformed NT-proBNP on admission	T	p-value
Age	7.280	0.000
Time to blood drawing at admission	7.044	0.000
Gender	-5.422	0.000
Ejection fraction (echocardiography)	-4.697	0.000
cTnT at admission	3.742	0.000
Persistent Angina pectoris at admission	-2.583	0.010
Heart rate at admission	2.400	0.017
ST-elevation at admission	-2.153	0.032
History of CAD	1.399	0.163
TIMI flow before PCI	-1.300	0.194
Systolic blood pressure at admission	-0.870	0.385
Number of diseased vessels	0.799	0.425
Body mass index	-0.522	0.602
Cardiogenic shock	0.272	0.786
Dependent Variable logarithmically transformed NT-proBNP at day 1	**T**	**p-value**
Ejection fraction (echocardiography)	-6.609	0.000
Age	5.654	0.000
Gender	-5.332	0.000
Persistent Angina pectoris at admission	-3.741	0.000
cTnT at day 1	2.881	0.004
Heart rate at admission	2.309	0.022
TIMI flow before PCI	-1.949	0.052
TIMI flow after PCI	1.873	0.062
Body mass index	-1.502	0.134
Cardiogenic shock	1.455	0.147
History of CAD	1.343	0.180
Time to blood drawing at day 1	1.282	0.201
Systolic blood pressure at admission	-1.208	0.228
ST-elevation at admission	0.537	0.592
Number of diseased vessels	0.370	0.712

higher values of NT-proBNP assessed 0-3 hours, 3-6 hours and 6-12 hours after the onset of symptoms in patients with NSTEMI. For NT-proBNP assessed 12-24 hours and 24-48 hours after the onset of symptoms, we found no difference between NSTEMI and STEMI *(Table 4)*.

Figure 3.
NT-proBNP values in patients with unstable angina pectoris (UAP), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). Grey bars NT-proBNP on admission, black bars NT-proBNP at day 1. Values are expressed as median and the 75th percentile.

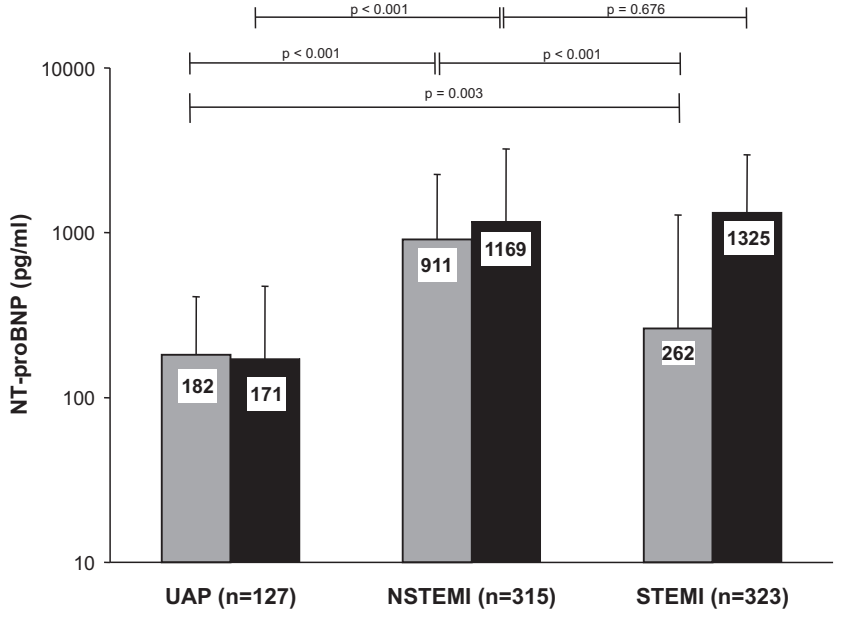


Table 4. NT-proBNP values on admission and at day 1 in patients with NSTEMI and STEMI with respect to the time delay from the onset of symptoms until blood drawing. Values for NT-proBNP are given as median (interquartile range) and value for the time delay as mean ± SD.

	NSTEMI			STEMI			
	n	NT-proBNP (pg/ml)	time delay (h)	n	NT-proBNP (pg/ml)	time delay (h)	p-value
NT-proBNP on admission							
0-3h	31	282 (89-918)	2.1 ± 0.5	123	127 (57-409)	2.2 ± 0.6	0.040
3-6h	44	825 (191-2080)	4.6 ± 0.7	84	189 (91-1337)	4.64± 0.8	0.002
6-12h	79	745 (284-2025)	8.7 ± 1.6	67	528 (187-1469)	8.6 ± 1.8	0.040
12-24h	112	1125 (477-2417)	17.8 ± 3.8	36	981 (467-2283)	16.2 ± 3.1	0.934
24-48h	49	1241 (731-4092)	31.1 ± 6.2	13	1495 (555-3146)	32.6 ± 6.6	0.924
NT-proBNP at day 1							
0-24h	61	1296 (588-3958)	18.8 ± 3.5	79	892 (376-2084)	18.4 ± 3.4	0.047
24-36h	106	1395 (584-3820)	29.9 ± 3.7	124	1594 (597-3110)	28.8 ± 3.7	0.807
36-48h	58	1138 (465-2686)	41.4 ± 3.4	25	2033 (1056-3078)	40.1 ± 3.3	0.093
48-72h	17	808 (318-1504)	52.8 ± 5.7	8	2172 (406-3013)	54.3 ± 5.2	0.406

NT-proBNP at day 1

The second sample for NT-proBNP assessment at day 1 was available from 555 patients (73%). There was no difference between those patients with and without the second sample available concerning NT-proBNP values on admission, age, gender, persistent angina pectoris on admission, history of CAD, ejection fraction, troponin T on admission, time interval from the onset of symptoms until admission, and the frequency of the diagnosis of NSTEMI and STEMI.

Duration from the onset of symptoms until second blood drawing at the day following admission was shortest in the group of patients with STEMI and UAP and was longer in patients with NSTEMI. Patients were divided into groups according to duration from the onset of symptoms to the second blood drawing at day 1 (0-24 h; 24-36 h; 36-48 h; 48-60 h; 60-72 h). Similarly to the results on admission, values for NT-proBNP at day 1 were lower in the group of patients in whom the second blood drawing was performed within 24 hours after the onset of symptoms compared to the patients in whom blood drawing was performed 24-36 hours after the onset of symptoms. In the other groups, in which the duration till blood drawing was beyond 36 hours, there was no difference in NT-proBNP values with respect to duration from the onset of symptoms. Consistently, in both sampling periods the highest values for NT-proBNP were found 24-36 hours after the onset of symptoms *(Figure 1)*.

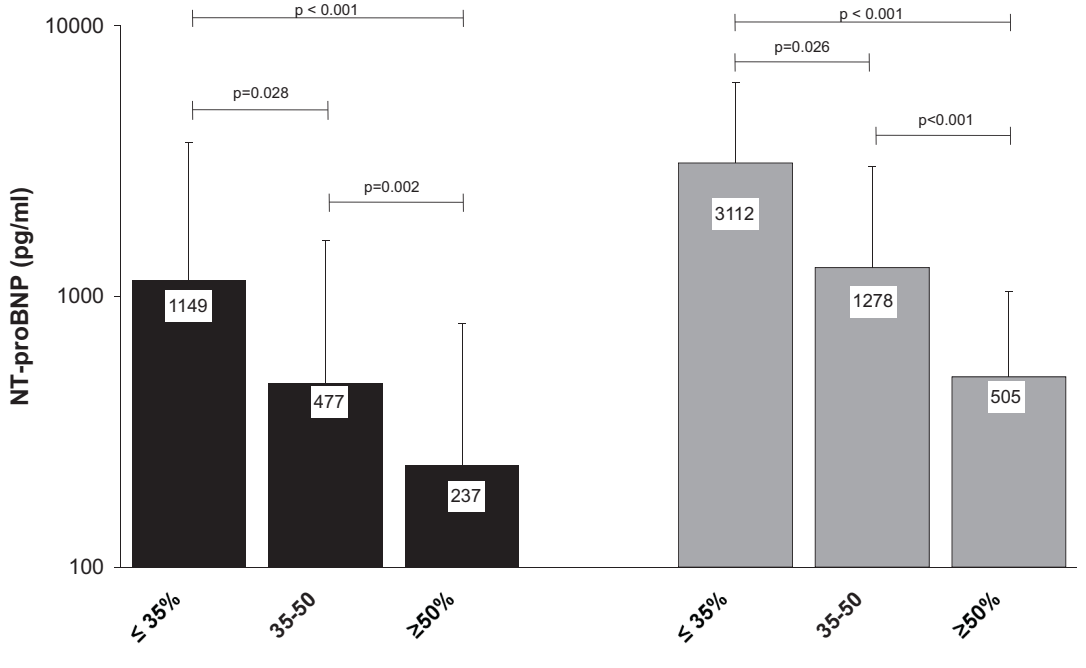
Female gender, age above 65 years (median), a left ventricular ejection fraction below 45%, a blood pressure below 100 mm Hg, a heart rate above 100 bpm, a positive troponin T test, the presence of ST-elevation in the ECG, the presence of a cardiogenic shock and an occluded infarct related artery (TIMI 0 or I flow) were associated with higher values for NT-proBNP in the second samples (Table 2). However, in a multivariate analysis, only gender, age, ejection fraction, heart rate, cTnT at day 1 and persistent angina pectoris on admission remained independent determinants for NT-proBNP *(Table 3)*.

Even though values for NT-proBNP on admission of patients with NSTEMI were higher than the values of patients with STEMI, there was a more pronounced increase in patients with STEMI, so that the values of NT-proBNP at day 1 were not different in both groups of patients. In contrast, NT-proBNP values of patients with UAP on admission were lowest compared to NSTEMI and STEMI and did not change significantly from admission to day 1 *(Table 1, Figure 3)*.

Relation of NT-proBNP to left ventricular ejection fraction and cardiac markers

Left ventricular ejection fraction assessed by echocardiography was found to be a strong determinate in uni – and multivariate analysis for NT-proBNP values on admission and at day 1 with highest values in patients with lowest ejection fraction and vice versa *(Table 2 and 3, Figure 4)*. There was a negative correlation between left ventricular ejection fraction and NT-propBNP values on admission (Spearman rho = -0.331, p<0.001) and

Figure 4. Relation of NT-proBNP to the left ventricular ejection fraction assessed by echocardiography. Black bars NT-proBNP on admission, grey bars NT-proBNP at day 1. Values are expressed as median and the 75th percentile.

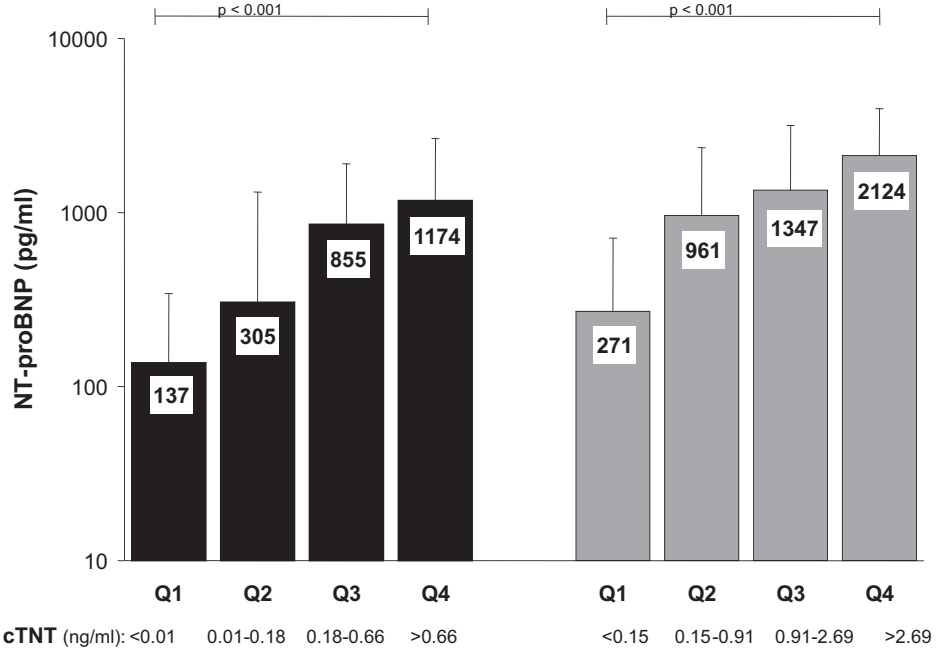


to NT-proBNP on day 1 (Spearman rho = -0.509, p<0.001).

NT-proBNP on admission was positively correlated to troponin T on admission, (Spearman Rho = 0.474, p<0.001) and NT-proBNP assessed at day 1 was equally correlated to troponin T at day 1 (Spearman Rho=0.486, p<0.001). NT-proBNP values on admission and at day 1 were related to quartiles of troponin T, with increasing values of NT-proBNP and increasing quartiles of cTnT *(Figure 5)*. NT-proBNP on admission and on day 1 was weaker, but still significantly correlated to the respective values of CK MB (Spearman Rho=0.326, p<0.001 and Rho=0.341, p<0.01) and myoglobin (Spearman Rho=0.076, p=0.035 and Rho=0.455, p<0.001).

findings of time-dependent changes of BNP after acute myocardial infarction with peak values 20.6 hours respectively 24 hours after the onset of symptoms (22,23). Consistent with our results are the findings reported in a substudy of the FRISC II trial on serial NT-proBNP measurement in patients with acute coronary syndromes. Here, the highest values were measured at study inclusion with a median delay after the onset of symptoms of 38 hours and a continuous decrease in NT-proBNP after 48 hours and during further follow up (24). However, this study provides no data on NT-proBNP values in the very early phase. The observed release kinetics in patients with an ACS is also consistent with experimental data of a rat myocardial infarction

Figure 5. Relation of NT-proBNP to quartiles of troponin T assessed on admission (black bars) and at day 1 (grey bars). Values are expressed as median and the 75th percentile.



DISCUSSION

The main finding of the present study is the dependency of NT-proBNP values on duration from the onset of symptoms. NT-proBNP values were within the normal range in those patients presenting within the first three hours after the onset of symptoms and the highest values were observed after 24 to 36 hours. Thus, peak values of NT-proBNP were in most cases not seen in the samples taken on admission but at the day following admission.

The time-dependent dynamics of NT-proBNP values observed in this study is similar to findings of elevated BNP values after percutaneous transluminal coronary angioplasty with an increase 4-8 hours and peak values 24 hours after transient ischemia caused by balloon inflation (21) and

model, in which it was found, that BNP mRNA expression in the ventricles increases 4 hours after myocardial infarction with a maximum increase after 12 hours (10).

These findings gain additional relevance, since assessment of natriuretic peptides, e.g. BNP or NT-proBNP in the emergency room have been advocated in patients with myocardial infarction (25,26). Our data show that the time interval from the onset of symptoms until blood drawing has to be considered for the interpretation of NT-proBNP values in patients with ACS. The results of all these studies raise the question of the optimal timing for BNP and NT-proBNP assessment. Since BNP and NT-proBNP de novo synthesis and release in response to myocardial ischemia is detectable only with a delay of 3-4 hours and under the assumption

that the extent of myocardial ischemia is best reflected by peak values of NT-proBNP, our data would suggest that the optimal timing for risk stratification is 24-36 hours after the index event. It remains an open issue whether the peak value of NT-proBNP is a better predictor for an adverse outcome than previous measurements on admission. In the future, studies on the predictive value of serial NT-proBNP testing should be performed with a sample taken 24 to 36 hours after the onset of symptoms in addition to baseline assessment.

In the present study, we assessed NT-proBNP values in patients presenting with the entire spectrum of ACS reaching from UAP to NSTEMI and STEMI. Each of these subgroups had a distinct pattern of NT-proBNP change from admission to the day following admission. Patients with UAP had NT-proBNP values on admission, which were within the normal range, below the 95th percentile of healthy blood donors, and there was no change from baseline to the second assessment the following day. In contrast, patients with NSTEMI had the highest admission values of NT-proBNP with a moderate increase from baseline to day one. Patients presenting with STEMI had comparably low NT-proBNP values on admission, but a marked increase and at day 1 NT-proBNP values of patients with STEMI and NSTEMI were almost identical. Thus, the relation of the time delay after the onset of symptoms until NT-proBNP assessment has to be considered especially in the group of patients admitted very early. Our findings are in agreement with observations of Galvani et al. (27) who investigated the prognostic value of NT-proBNP across the whole spectrum of ACS and found higher NT-proBNP values in patients with NSTEMI and a 1.8 times lower cut-off for NT-proBNP in patients with STEMI. The differences in the release pattern of NT-proBNP in NSTEMI and STEMI can in part be explained with the time-dependent dynamics of NT-proBNP changes. Nevertheless, after correcting the time delay from the onset of symptoms, NT-proBNP values were higher for patients with NSTEMI if assessed within 12 hours after the onset of symptoms. Therefore, additional contributing factors for NT-proBNP elevation in NSTEMI have to be present. Recently, several studies have consistently demonstrated that BNP and NT-proBNP are related to the extent of myocardial ischemia in CAD and might reflect recurrent ischemic episodes (7,28). Thus, higher admission values of NT-proBNP in NSTEMI might be the result of myocardial ischemia preceding the index event. In addition, cytokine activation, which is known to increase BNP and NT-proBNP levels (29), may be considered to account for the difference in release pattern of NT-proBNP in patients with NSTEMI and STEMI.

In healthy individuals and patients with various cardiovascular disorders like congestive heart failure and aortic valve stenosis, it is established that BNP and NT-proBNP levels are dependent on gender with higher values of females, on age with higher values in the elderly patients and on left ventricular function (30-32). In our study on patients with ACS, we observed the same association between NT-proBNP and gender, age and left ventricular function. It is generally accepted that increased myocardial stretch is the underlying mechanism for increased BNP and NT-proBNP values in patients with left ventricular dysfunction. The reasons for the relation between BNP and NT-proBNP and age and gender are unknown, but differences in metabolism and elimination are discussed as well as a difference in the myocardial synthesis rate.

CONCLUSION

The time interval from the onset of symptoms until NT-proBNP assessment is a major determinant for NT-proBNP values on admission of patients with an acute myocardial infarction, either NSTEMI or STEMI and the time-dependent dynamics of NT-proBNP needs to be considered for the interpretation of individual values. To achieve the peak elevation of NT-proBNP, sequential testing with a second sample 24 to 36 hours after the index event has to be performed. However, it remains an open issue whether maximum values of NT-proBNP are of superior predictive value. We also did observe different release patterns of NT-proBNP for patients with UAP, NSTEMI and STEMI, with highest admission values in NSTEMI but no difference of NT-proBNP values assessed the following day between patients with STEMI and NSTEMI. This can in part be explained by the time-dependent release of NT-proBNP. Thus, these findings require further studies, which evaluate the incremental diagnostic and prognostic information of a strategy of sequential testing compared to a single measurement.

Limitations

In the present study, most of the patients were under a standard medication, which might have impact on the measured NT-proBNP values. However, the medication on admission has not been assessed. Thus, we were not able to analyse the influence of specific drugs on NT-proBNP. Moreover, we did not consider in our database whether patients had atrial fibrillation. Thus, we

were not able to analyse the impact of atrial fibrillation on NT-proBNP values in patients with acute coronary syndromes.

Acknowledgements

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KINETIKA OSLOBAĐANJA N-TERMINALNOG PRO B-TIPA NATRIURETIČNOG PEPTIDA (NT-proBNT) KOD AKUTNIH KORONARNIH SINDROMA

Michael Weber, Christian Kleine, Eva Keil, Matthias Rau, Alexander Berkowitsch, Albrecht Elsaesser, Veselin Mitrović, Christian Hamm

Kerkof Centar za srce, Kardiološko odeljenje, Bad Nojham, Nemačka

SAŽETAK

Nedavno je utvrđeno da BNP i NT-proBNT pružaju nezavisnu prognostičku informaciju o pacijentima sa akutnim koronarnim sindromom (ACS). Međutim, malo podataka je dostupno o vremenskom trajanju NT-proBNT nivoa u pogledu početka javljanja simptoma.

Studija je uključila 765 pacijenata (236 ženskog pola, starosne dobi 64±11 godina) sa ACS (STEMI 42%, NSTEMI 41%, UAP 17%) koji su upućeni na koronarnu angiografiju. NT-proBNT je procenjen na prijemu i narednog dana. NT-proBNT vrednosti odnosile su se na vremensko trajanje od početka javljanja sindroma do davanja krvi, sa najnižim vrednostima u prva tri sata i najvišim vrednostima u okviru 24-36 sati nakon javljanja simptoma (147 (64-436) pg/ml i 1099 (293-3795) pg/ml, p<0.001). Najviše vrednosti NT-proBNT na prijemu su određene kod pacijenata sa NSTEMI u poređenju sa pacijentima sa STEMI i UAP (912 (310-2258) pg/ml) za razliku od 262 (85-1282) pg/ml i 182 (74-410) pg/ml; p<0.001), dok razlika nije uočena između STEMI i NSTEMI dan nakon prijema (1325 (532-2974) pg/ml nasuprot 1169 (555-3413) pg/ml; p 0.676). Za razliku od toga, NT-proBNT vrednosti su ostale nepromenjene kod UAP (182 (74-410) pg/ml nasuprot 171 (53-474) pg/ml).

Vremenski interval od početka javljanja simptoma do prvog davanja krvi je važna determinanta za određivanje NT-proBNT vrednosti na prijemu pacijenata sa ACS i treba je razmotriti u kliničkoj praksi.

Ključne reči: **N-terminalni pro-B tip natriuretični peptid, NT-proBNP, akutni koronarni sindrom, infarkt miokarda**