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Release kinetics of N-terminal pro-B-type natriuretic peptide in a clinical model of acute myocardial infarction

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ABSTRACT

Background: N-terminal segment of B-type natriuretic peptide prohormone (NT-proBNP) is elevated in patients with acute myocardial infarction (AMI) thus providing both diagnostic information and prognostic information. The aim of the present study was to determine the time course of NT-proBNP release in patients undergoing transcoronary ablation of septal hypertrophy (TASH) a procedure mimicking AMI.
Methods: We analyzed the release kinetics of NT-proBNP in 18 consecutive patients with hypertrophic obstructive cardiomyopathy undergoing TASH. Serum samples were collected prior to and at 15, 30, 45, 60, 75, 90, and 105 min, and 2, 4, 8, and 24 h after TASH.
Results: NT-proBNP concentrations showed a continuous increase during the first 75 min with a significant percent change compared to baseline value already 15 min after TASH (105.6% [IQR 102.2–112.7]; $P < 0.001$). All patients had a significant increase of NT-proBNP at 45 min (range of percent increase [min–max]: 103.5–137.2%; range of absolute increase [min–max]: 23.5–304.0 ng/L). NT-proBNP concentrations decreased below the baseline value until the 8th h after initiation of myocardial infarction.
Conclusion: NT-proBNP concentration increases immediately after induction of myocardial infarction proving early evidence of myocardial injury despite the decrease of the left ventricular wall stress due to the TASH related reduction of the left ventricular outflow gradient.

1. Introduction

Persistent myocardial ischemia leads to myocardial necrosis resulting in transient or permanent myocardial dysfunction. The release of B-type natriuretic peptide (BNP) and the amino-terminal equimolar fragment of its precursor hormone pro BNP (NT-proBNP) in patients with acute myocardial infarction (AMI) is based on both triggered directly by myocardial ischemia as well as increased wall stress caused by volume expansion and pressure overload due to impaired ventricular function [1–3]. Furthermore, several other pathophysiological mechanisms trigger the secretion of natriuretic peptides from cardiomyocytes such as ventricular hypertrophy, inflammation, fibrosis and myocardial ischemia/hypoxia [4].

NT-proBNP has emerged as powerful biomarker in various cardiovascular diseases and it is established for the diagnosis and prognosis of acute and chronic heart failure [5,6]. In head-to-head comparisons, BNP and NT-proBNP showed similar sensitivity and specificity for evaluation of symptomatic patients [7]. Whereas NT-proBNP is superior to BNP for the detection of asymptomatic patients with left ventricular dysfunction [8]. Additionally natriuretic peptides are also predictors of short- as well as long-term morbidity and mortality after AMI. This prognostic value was shown independently of myocardial dysfunction, diastolic contracture or regional wall motion abnormalities [9,10]. Furthermore, NT-proBNP concentrations correlate with the infarct size, the number of diseased coronary arteries and left ventricular remodeling [11–13].

Elevated NT-proBNP concentrations in patients with AMI are proven to be mainly reversible except for patients developing chronic heart failure [14]. In this context, serial measurement of NT-proBNP in patients with acute coronary syndrome can be used to identify patients at risk [15]. However, the best time point to determine NT-proBNP still remains unclear [14,16]. Because of the inaccurate definition of the exact time point of the onset of myocardial ischemia and patient-related delay before presentation to the hospital, the early release kinetics of NT-proBNP is not well described. Regarding the impact of natriuretic peptides on patient's outcome the knowledge of the exact release kinetics

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of NT-proBNP following AMI could improve the interpretation of the concentrations on admission and the risk stratification in patients with AMI.

Thus, the aim of the present study was to characterize the time course of NT-proBNP release in patients undergoing transcoronary ablation of septal hypertrophy (TASH) as a correlate for patients with AMI.

2. Material and methods

From March 2010 until June 2011, 18 consecutive patients with hypertrophic obstructive cardiomyopathy (HOCM) undergoing TASH were included in the study. Pre- and post-procedural management of the patients is published recently [17–19]. In brief, clinical history, physical examination, 12-lead ECG, laboratory tests, echocardiography, and coronary angiography for all patients were assessed. The final diagnosis of HOCM was made according to the current guidelines based on severe symptoms during daily activity, asymmetrical septal hypertrophy >15 mm, systolic anterior movement of the mitral valve, and an intraventricular pressure gradient of ≥30 mm Hg at rest and/or >50 mm Hg after provocation by the Valsalva maneuver [20]. TASH was performed according to standard clinical practice with temporary septal branch occlusion for selective therapeutic injection of 96% ethanol. Post-procedural management included monitoring at the intensive care unit for 48 h. All patients enrolled in the study signed informed consent, which included consent for biomarker analyses. The ethical board of the state of Hessen, Germany, approved the study (FF 31/2010).

2.1. Laboratory assessment

Venous blood samples for determination of NT-proBNP were collected in plain tubes before and at 15, 30, 45, 60, 75, 90, and 105 min, and 2, 4, 8, and 24 h after induction of myocardial infarction. Serum was processed immediately and frozen at −80 °C until assayed. The median time of storage at −80 °C until NT-proBNP measurement was 22.5 months (IQR 17.3–28.8 months). Samples were thawed for the first time directly before measuring NT-proBNP to reduce assay imprecision. The in vitro degradation of NT-proBNP was not tested.

NT-proBNP was measured in serum with an electrochemiluminescence immunoassay using monoclonal antibodies (NT-proBNP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The lower detection limit for the NT-proBNP assay is 5.0 ng/L and concentrations above the measuring range are reported as >35 000 ng/L. The lowest concentration measurable with a coefficient of variation (CV) of 20% for this assay is 50.0 ng/L. At the cut-off value 150 ng/L the CV is <3%. The upper limit of normal is 300.0 ng/L.

2.2. Statistical analysis

All data for continuous variables are expressed as mean ± SD or as median and interquartile range as appropriate. Categorical variables are reported as number and percentage. The data are distributed non-parametrically as tested by Kolmogorov–Smirnov-test. Continuous variables were compared using the Wilcoxon signed-rank test. All statistical tests were performed with SPSS software, version 19.0. A two-tailed P value <0.05 was considered to be statistically significant.

3. Results

Clinical and procedural characteristics of all patients (10 men, 8 women, mean [SD] age 61.7 [13.1] y) enrolled in the study have been previously described and are presented in Table 1 [13–15]. All TASH procedures were performed in a single-session procedure using a single septal branch occlusion. During the procedure the mean (SD) administered ethanol was 1.7 (0.4) mL. The median occlusion time was 17.0 min (IQR 12.5–23.8). The median occlusion time was 17.0 min (IQR 12.5–23.8). At baseline 14 (77.8%) patients showed elevated NT-proBNP (min–max: 255.5–8737.0 ng/L).

Table 1
Baseline characteristics of 18 patients undergoing transcoronary ablation of septal hypertrophy.

Variable	(n = 18)
Age (years)	61.7 ± 13.1
Male, n (%)	10 (55.6)
Body mass index (kg/m2)	29.8 ± 5.7
Cardiovascular risk factors, n (%)	
Current smoking	8 (44.4)
Hypertension	10 (55.6)
Hypercholesterolemia	5 (27.8)
Diabetes mellitus	3 (16.7)
Family history	4 (22.2)
NYHA class	2.7 ± 0.5
CCS class	1.8 ± 0.8
Laboratory measurements	
Creatinine (μmol/L)	67.8 IQR (65.1–71.3)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	92.3 IQR (80.2–116.5)

Measurement of serum NT-proBNP concentrations revealed a continuous increase during the first 75 min in all patients with a significant percent change compared to baseline value already 15 min after induction of MI (105.6% [IQR 102.2–112.7]; P < 0.001). All patients had a significant increase of NT-proBNP compared to baseline value at 45 min (range of percent increase [min–max]: 103.5–137.2%; range of absolute increase [min–max]: 23.5–304.0 ng/L). NT-proBNP concentrations started to decrease at the 75th min and decreased below the baseline value until the 8th h after initiation of myocardial infarction. In 11 (61.1%) patients NT-proBNP concentrations were increased at 24 h after TASH (Fig. 1). The NT-proBNP concentrations and minimum/maximum concentrations at each of the different time points are shown in Table 2. Additionally, no sex specific differences between the rates of increase could be observed for NT-proBNP. The intraventricular pressure gradient at rest and after provocation by the Valsalva maneuver was significantly decreased after TASH. The echocardiographic characteristics of all patients before and after TASH are presented in Table 3.

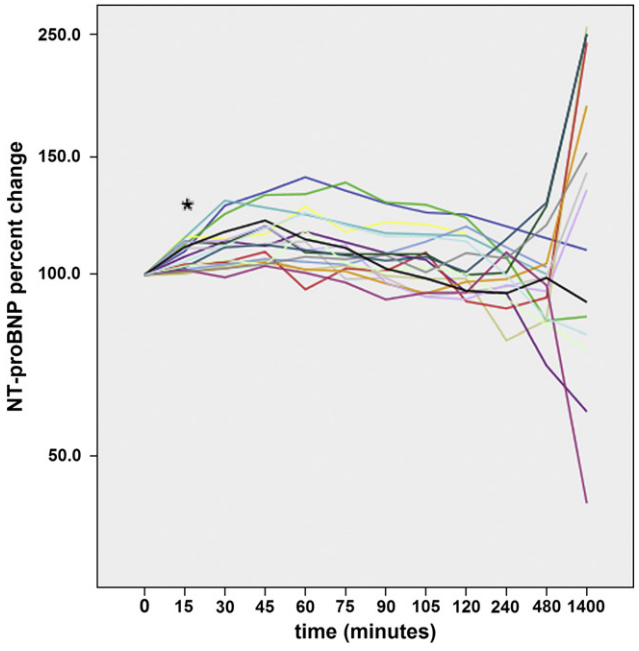

Fig. 1. NT-proBNP values with percent change of all patients throughout the study. The asterisk indicates the first time point with significant median increase (P < 0.05) compared to baseline value.