B-Type Natriuretic Peptide and its Molecular Precursor in Myocardial Infarction Complicated by Cardiogenic Shock

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ABSTRACT

Background: Plasma measurement of cardiac natriuretic peptides and their biosynthetic precursors is helpful in chronic heart failure patients. In contrast, information on circulating B-type natriuretic peptide (BNP) and its molecular precursor (proBNP) in patients with cardiogenic shock is scarce. We therefore examined proBNP-derived peptides in plasma from patients with myocardial infarction complicated by cardiogenic shock.

Methods and Results: Patients were referred for early, invasive therapy because of myocardial infarction complicated by cardiogenic shock (n = 13). Plasma proBNP was measured with an automated assay (NT-proBNP) and an in-house radioimmunoassay (proBNP); BNP concentrations were quantitated with an immunoradiometric assay. The median NT-proBNP concentration was 8.2-fold higher than the corresponding BNP concentration (873 pmol/L [range 41−12,486] versus 107 pmol/L [1−1041], $P < .001$). Moreover, the NT-proBNP concentration was 3.3-fold higher compared with proBNP (268 pmol/L [19−12,220], $P < .01$). Despite the molar differences, there was a strong correlation between NT-proBNP and proBNP ($r = 0.84$, $P < .0001$) and BNP ($r = 0.82$, $P < .0001$) concentrations. Gel filtration chromatography suggested that the proBNP immunoreactivity reflect a molecular form larger than the N-terminal 1-76 fragment.

Conclusions: The study reveals the plasma profile of proBNP-derived peptides during myocardial infarction complicated by cardiogenic shock. Peripheral concentrations of NT-proBNP, proBNP, and BNP were highly correlated despite marked differences between assays. The results also suggest an increase in cardiac proBNP processing after myocardial infarction and cardiogenic shock. (*J Cardiac Fail 2007;13:184−188*)

Key Words: BNP, Cardiogenic shock, Myocardial infarction, Natriuretic peptide, proBNP.

Plasma measurement of the cardiac natriuretic peptides and their biosynthetic precursors has proven useful in chronic heart failure patients. In particular, normal concentrations can exclude a diagnosis of reduced left ventricular function and aid the clinician in sorting cardiovascular disease from other conditions in patients presenting with dyspnea.[1,2] Both B-type natriuretic peptide (BNP) and N-terminal fragments from its biosynthetic precursor seem to be useful markers. Nevertheless, plasma concentrations of the different proBNP-derived peptides vary markedly in healthy persons and in heart failure patients, which is thought to mainly reflect differences in elimination. A few head-to-head studies comparing BNP and proBNP as marker of left ventricular dysfunction have demonstrated equal diagnostic as well as prognostic performance using automated assays.[3−5] Quantification of either the N-terminal proBNP 1-76 fragment (referred to as NT-proBNP) or the C-terminal BNP hormone therefore seems to parallel each other in heart failure diagnostics although the circulating concentrations differ.[6]

In contrast to chronic heart failure patients, the present information of circulating proBNP-derived peptides in patients with myocardial infarction complicated by cardiogenic shock is still scarce. This dismal condition is associated with a high mortality even if intensively treated with early, invasive revascularization, and intra-aortic balloon counterpulsation supporting the coronary blood flow.[7] Only a few studies have focused on the association

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between increased plasma BNP or proBNP concentrations and development of cardiogenic shock in heart failure patients or in diabetic patients after myocardial infarction.[8,9] Furthermore, the cardiac secretion of natriuretic peptides per se in cardiogenic shock has not been elucidated and the molecular heterogeneity of proBNP-derived peptides in plasma is not resolved in this complex condition.[10] In the present study, we therefore examined proBNP-derived peptides in plasma from a small group of patients with acute myocardial infarction complicated by cardiogenic shock. Specifically, we aimed at establishing whether the severely failing heart still possesses an endocrine capability in mounting a natriuretic response.

Methods

Patients

Patients were referred from local hospitals to our central intensive care unit for invasive treatment of cardiogenic shock. The inclusion criteria for this study were 1) myocardial infarction (minimum 2 of 3 criteria: electrocardiogram changes, chest pain, or troponin/creatinine kinase isoform MB elevation) within the previous 48 hours; 2) development of cardiogenic shock after onset of myocardial infarction defined as systolic blood pressure < 90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure > 90 mm Hg; and 3) clinical symptoms including cold clammy extremities, reduced renal function defined as oliguria or anuria, high respiratory rate, shallow respiration, sinus tachycardia, or a change in mental status. All the listed criteria had to be present in each individual patient. The study was approved by the local ethics committee (KF01-066/01). Clinical data including the medical history before referral, treatment offered before and after early revascularization, and hemodynamic profile, renal status, and short-term outcome after treatment were obtained daily from admittance to day 6.

Peptide Measurements

Peripheral venous blood was obtained immediately at arrival to the intensive care unit before any additional therapy was instituted. A second sample was obtained at day 1 or 2 followed by a new sample at day 6. All samples were collected in EDTA containing Vacutainers, immediately centrifuged, and the plasma stored at −80°C until further analysis. Plasma NT-proBNP concentrations were measured with an automated assay (Roche Modular, Roche Diagnostics, Hvidovre Denmark). The proBNP concentrations were quantitated using an in-house radioimmunoassay; the validation of this assay has been reported previously.[11] In brief, this method quantifies the total concentration of the intact precursor (proBNP 1-108) and the N-terminal fragment (proBNP 1-76) after a preanalytical enzymatic step.[12] Assay imprecision (within-runs) is 12% at 13 pmol/L and 5% at 130 pmol/L.[11] Finally, plasma BNP concentrations were measured with a commercial immunoradiometric assay (Shionoria BNP, Osaka, Japan). This assay detects BNP-32 with no reported cross-reactivity to proBNP. Lowest level of detection is 0.6 pmol/L (1 pmol/L equals 3.46 pg/mL), and assay imprecision according to the manufacturer is 2.7% at 6.4 pmol/L and 2.0% at 149 pmol/L within-runs. All samples were measured in duplicate and in the same batch.

Gel Filtration Chromatography

Plasma was applied to a 1000 × 10 mm Sephadex G-50 Superfine column (Pharmacia, Uppsala, Sweden) and eluted at 4°C in a Tris buffer containing 0.2% human serum albumin and 0.2 mol/L NaCl at pH 8.5 (flow rate 4 mL/h). The column was calibrated in a separate run with synthetic proBNP 1-76 (Phoenix Peptides, Karlsruhe, Germany); void and total volumes were determined by the elution of ^{125}I-albumin and ^{22}NaCl, respectively.

Statistical Analyses

Discrete variables are presented as percentages and continuous variables are listed as median values with ranges unless otherwise stated. Linear regression analyses were performed on transformed (log10) as a normal distribution could not be presumed. Comparison between assays was performed using the Krustal-Wallis test except from comparison of the BNP to proBNP ratio between days, where the Wilcoxon signed-rank test was used. The 2-tailed significance level of the type 1 error was set at 0.05.

Results

In the study period, 36 patients were referred with cardiogenic shock. Of these, 23 patients did not meet the inclusion criteria either because of late referral (>48 hours after myocardial infarction) or hemodynamic shock superposing a diagnosis of chronic heart failure. Thus 13 patients fulfilled the inclusion criteria and constituted the present study population. Table 1 shows the baseline characteristics of the included patients. The population consisted mainly of by male subjects and the average time from myocardial

Table 1. Patient characteristics at arrival, clinical treatment, and outcome

Baseline variables	Values
Age (y)	66 (37−77)
Female gender	2/13
History of	
- Prior myocardial infarction	11/13
- Diabetes	4/13
- Hypertension	1/13
Clinical status	
- Anterior infarction	8/13
- Thrombolysis	8/13
- Diuresis (mL/h)	0 (0−130)
- Serum creatinine (mg/dL)	1.73 (0.72−4.70)
- Base excess	−7 (−9 to −2)
- Systolic blood pressure (mm Hg)	80 (50−105)
- Diastolic blood pressure (mm Hg)	51 (30−70)
- Heart rate (beats/min)	100 (62−30)
- Transcutaneous arterial O_2 sat (%)	93 (78−98)
- SvO_2 (%)	54 (42−58)
- Left ventricular ejection fraction (%)	20 (10−50)
Clinical strategy	
- Inotropic/pressure treatment	12/13
- Mechanical ventilation	4/13
- Intraaortic blood pressure	5/13
- PCI	10/13
Clinical outcome	
- Mortality in the department	5/13

Numerical data are expressed as median with ranges.

S_VO_2, central venous oxygen saturation; PCI, percutaneous coronary intervention.