CLINICAL RESEARCH STUDY

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B-type Natriuretic Peptide in the Early Diagnosis and Risk Stratification of Acute Chest Pain

Philip Haaf, MD,[a]* Tobias Reichlin, MD,[a]* Nils Corson, MD,[a] Raphael Twerenbold, MD,[a] Miriam Reiter, MD,[a] Stephan Steuer, MD,[b] Stefano Bassetti, MD,[c] Katrin Winkler, MD,[d,e] Claudia Stelzig, MSc,[a] Corinna Heinisch, MD,[a] Beatrice Drexler, MD,[a] Heike Freidank, MD,[f] Christian Mueller, MD, FESC[a]

[a]Department of Internal Medicine, University Hospital, Basel, Switzerland; [b]Department of Emergency Medicine, Spital Limmattal, Schlieren, Switzerland; [c]Department of Internal Medicine, Kantonsspital Olten, Olten, Switzerland; [d]Servicio de Pneumologia, Hospital del Mar - IMIM, UPF, CIBERES, ISC III and [e]Servicio de Urgencias, Hospital del Mar - IMIM, Barcelona, Spain; [f]Department of Laboratory Medicine, University Hospital, Basel, Switzerland.

ABSTRACT

BACKGROUND: Myocardial ischemia is a strong trigger of B-type natriuretic peptide (BNP) release. As ischemia precedes necrosis in acute myocardial infarction, we hypothesized that BNP might be useful in the early diagnosis and risk stratification of patients with acute chest pain.

METHODS: In a prospective, international multicenter study, BNP was measured in 1075 unselected patients with acute chest pain. The final diagnosis was adjudicated by 2 independent cardiologists. Patients were followed long term regarding mortality.

RESULTS: Acute myocardial infarction was the adjudicated final diagnosis in 168 patients (16%). BNP levels at presentation were significantly higher in acute myocardial infarction as compared with patients with other diagnoses (median 224 pg/mL vs. 56 pg/mL, $P < .001$). The diagnostic accuracy of BNP for the diagnosis of acute myocardial infarction as quantified by the area under the receiver operating characteristic curve (AUC) (0.74; 95% confidence interval [CI], 0.70-0.78) was lower compared with cardiac troponin T at presentation (AUC 0.88; 95% CI, 0.84-0.92; $P < .001$). Cumulative 24-month mortality rates were 0.5% in the first, 2.1% in the second, 7.0% in the third, and 22.9% in the fourth quartile of BNP ($P < .001$). BNP predicted all-cause mortality independently of and more accurately than cardiac troponin T: AUC 0.81 (95% CI, 0.76-0.86) versus AUC 0.70 (95% CI, 0.62-0.77; $P < .001$). Net reclassification improvement for BNP was 0.10 ($P = .04$), and integrated discrimination improvement 0.068 ($P = .01$).

CONCLUSIONS: BNP accurately predicts mortality in unselected patients with acute chest pain independently of and more accurately than cardiac troponin T, but does not seem to help in the early diagnosis of acute myocardial infarction.

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*P. Haaf and T. Reichlin contributed equally to this work.

Requests for reprints should be addressed to Christian Müller, MD, Department of Internal Medicine, University Hospital Basel, Petersgraben 4, Basel CH-4031, Switzerland.

E-mail address: chmueller@uhbs.ch

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B-type natriuretic peptide (BNP) has emerged as a quantitative marker of ventricular wall stress[1-3] and important clinical help in the early diagnosis of heart failure.[4-6] Experimental and clinical studies have demonstrated that myocardial ischemia and acute hypoxia are strong triggers of BNP release.[7,8] These observations were confirmed by clinical studies demonstrating an immediate increase in natriuretic peptide levels after transient myocardial ischemia induced by cardiac exercise testing.[9-11]

The early diagnosis of acute myocardial infarction is currently limited due to a delayed increase of circulating cardiac troponin levels within the first 4 to 6 hours after the onset of symptoms.[12] Therefore, it has been speculated that the additional use of natriuretic peptides as a marker of myocardial ischemia might improve the diagnostic accuracy at presentation and the management of patients.[13-15] Several studies showed increased levels of natriuretic peptides in patients with acute myocardial infarction but failed to convincingly demonstrate a clinically meaningful benefit in the diagnosis of acute myocardial infarction through the additional use of natriuretic peptides.[16-20] Because ischemia precedes necrosis in acute myocardial infarction, we hypothesized that BNP might be useful in the early diagnosis of patients with acute chest pain.

Several studies have established the prognostic value of BNP in patients with acute myocardial infarction and unstable angina.[21-23] The value of BNP in the risk stratification of unselected patients with acute chest pain, however, has been analyzed in only few studies for subgroups without ST-elevation myocardial infarction.[24] The second aim of the present study, therefore, was to assess the prognostic value of BNP in these patients and compare it with established prognostic markers such as cardiovascular risk factors, with established risk-stratification models[25] and with cardiac troponin T (cTnT).

CLINICAL SIGNIFICANCE

- B-type natriuretic peptide (BNP) levels of patients with acute myocardial infarction are higher than in other chest pain patients.
- The diagnostic accuracy of BNP for AMI is moderate.
- BNP is a powerful predictor of mortality in chest pain patients.
- Prediction of mortality of chest pain patients with BNP is more accurate than with cardiac troponin T.

METHODS

Study Design and Population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital, Basel, Switzerland.[26,27] From April 2006 to June 2009, a total of 1247 consecutive patients presenting to the Emergency Department with symptoms suggestive of acute myocardial infarction such as acute chest pain and angina pectoris were recruited. Of these, BNP values at presentation were available in 1075. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

Routine Clinical Assessment

All patients underwent an initial clinical assessment including clinical history, physical examination, 12-lead electrocardiogram (ECG), pulse oximetry, standard blood tests, and chest radiography. cTnT, the MB fraction of creatine kinase (CK-MB), and myoglobin were measured at presentation, and thereafter as long as clinically indicated. Timing and treatment of patients were left to the discretion of the attending physicians.

Adjudicated Final Diagnosis

To determine the causal diagnosis for each patient, 2 independent cardiologists reviewed all available medical records (including patient history, physical examination, results of laboratory and radiologic testing, ECG, echocardiography, cardiac exercise test, coronary angiography) pertaining to the patient from the time of Emergency Department presentation to 60-day follow-up. Cases were reviewed with a third cardiologist in situations of diagnostic disagreement.

Acute myocardial infarction was defined as recommended in current guidelines.[28] In brief, acute myocardial infarction was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Necrosis was diagnosed by a rising or falling (or both) pattern of cTnT with at least one value above the 99th percentile with an imprecision of $<10\%$.[26,27] Unstable angina was diagnosed in patients with normal cTn levels and typical angina at rest, a deterioration of a previously stable angina, in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have stenosis $\geq 70\%$, and in ambiguous cases in which follow-up information revealed acute myocardial infarction or a sudden unexpected cardiac death within 60 days. Further, predefined diagnostic categories included cardiac but not coronary symptoms (eg, perimyocarditis, tachyarrhythmias) and noncardiac symptoms. If acute myocardial infarction was excluded in the Emergency Department, but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as of unknown origin.