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Diagnostic utility of a single-epitope sandwich B-type natriuretic peptide assay in stable coronary artery disease: Data from the Akershus Cardiac Examination (ACE) 1 Study

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ABSTRACT

Objectives: To assess the merit of a novel single-epitope sandwich (SES) assay specific to the stable part of BNP in patients with reversible myocardial ischemia as post-translational modifications of BNP may influence assay performance.

Design and methods: We measured BNP concentration by a conventional assay and the SES-BNP assay in 198 patients referred for myocardial perfusion imaging (MPI). BNP concentration was determined before and immediately after exercise stress testing, and 1.5 and 4.5 h later. Patients were categorized according to MPI results.

Results: BNP concentration was higher with both assays at all time points in patients with reversible myocardial ischemia ($n=19$) compared to the other patients ($n=179$). Measuring BNP after stress testing or calculating the changes in BNP concentration did not improve diagnostic accuracy compared to baseline measurements: SES-BNP: AUC 0.71 (95% CI 0.58–0.84) vs. conventional BNP: 0.71 (0.59–0.83), $p=0.96$. By linear regression analysis, reversible myocardial ischemia was significantly associated with baseline SES-BNP concentration ($p=0.043$), but not with measurements by the conventional assay ($p=0.089$). In multivariate logistic regression models, only baseline measurement with the SES-BNP assay was significantly associated with reversible myocardial ischemia: odds ratio [logarithmical transformed BNP] 2.00 (95% CI 1.16–3.47), $p=0.013$. The SES-BNP assay, but not the conventional BNP assay, reclassified a significant proportion of the patients towards their correct category on top of the best clinical model of our data set: NRI = 0.47, $p=0.04$.

Conclusions: The SES-BNP assay was significantly associated with reversible myocardial ischemia as assessed by several statistical indices, while a conventional BNP assay was not.

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1. Introduction

Identifying patients with stable coronary artery disease (CAD) can be difficult. In a recent study of almost 400,000 patients undergoing non-urgent coronary angiography, only 37.6% were found to have obstructive CAD [1]. Furthermore, although stress testing had been performed in 84% of the patients prior to referral, 39% of these patients had no evidence of obstructive CAD. Hence, based on these data and other reports [2–4], there is a need for additional tools to diagnose patients with reversible myocardial ischemia.

B-type natriuretic peptide (BNP) is a 32 amino acid peptide derived from the C-terminal end of $proBNP_{1-108}$ (subscript indicative of amino acid position) [5]. In the traditional model of cardiomyocyte BNP production, $proBNP_{1-108}$ is processed to N-terminal $proBNP_{1-76}$

Abbreviations: BNP, B-type natriuretic peptide; SES-BNP assay, single-epitope sandwich BNP assay; MPI, myocardial perfusion imaging; AUC, area under the curve; CI, confidence interval; CAD, coronary artery disease; ACE 1 Study, Akershus Cardiac Examination 1 study; LV, left ventricular; ECG, electrocardiogram; METs, metabolic equivalents; LVEF, left ventricular ejection fraction; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; Q, quartile; ASA, acetyl salicylic acid; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ROC, receiver operating statistics; NRI, net reclassification index.

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and BNP_{1-32} in a 1:1 fashion [5]. Both BNP and NT-proBNP have previously been examined as biomarkers in patients with stable CAD [6]. However, recent experimental and clinical data have challenged the traditional model of BNP and NT-proBNP production by demonstrating that a substantial proportion of BNP immunoreactivity in plasma is found as uncleaved glycosylated $proBNP_{1-108}$ [7–9]. Moreover, $proBNP_{1-108}$ in plasma is not confined to patients with heart failure [10] and the release of uncleaved glycosylated $proBNP_{1-108}$ seems to represent the standard mechanism by which BNP is secreted from cardiomyocytes [11]. Of potential clinical relevance, current $proBNP_{1-108}$ immunoassays do not detect glycosylated molecules [9], thus assays with the capture and detection epitope in non-glycosylated parts of $proBNP_{1-108}$ may represent an advantage for natriuretic peptide measurement. The prevalence of truncated BNP_{1-32} molecules in plasma is also high [12], which could further compromise performance of BNP assays with antibodies specific to epitopes in the N- or C-terminal part of the peptide. Accordingly, in this study we wanted to test the hypothesis that a single-epitope sandwich (SES) assay with the capture and detection antibodies specific to the relatively stable non-glycosylated ring structure of BNP_{1-32} [13] would provide superior information to a conventional BNP assay in patients with reversible myocardial ischemia.

2. Methods

2.1. Study design

The Akershus Cardiac Examination (ACE) 1 study was a prospective study including 200 patients with suspected reversible myocardial ischemia referred to Akershus University Hospital, a teaching hospital in Norway, for myocardial perfusion imaging (MPI). All patients were assessed by a senior cardiologist for probability (0–100%) of reversible myocardial ischemia based on hospital records and current symptoms. We included patients between the age of 18 and 80 years according to a stratified protocol with 50 patients included from the low risk stratum (<33% probability), 100 patients from the intermediate risk stratum (33–67%), and 50 patients considered to be at high risk of reversible myocardial ischemia (>67% pre-test probability). The exclusion criteria of the study were inability or medical contraindications to perform a maximal bicycle stress test, left ventricular bundle branch block, and weight >120 kg. Patients with disseminated malignancies were not eligible for inclusion and two patients from the intermediate risk group were excluded shortly after stress testing as they were diagnosed with metastatic cancer. Hence, we obtained a final study cohort of 198 patients. We recorded information on comorbidities, history of CAD, and medication from the patients and from hospital records. We calculated left ventricular (LV) hypertrophy in the resting electrocardiogram (ECG) according to the criteria of Sokolow. We conducted the study according to the Declaration of Helsinki, the study was approved by the local Ethics Committee, and all patients provided informed consent before study commencement.

2.2. Exercise stress test and myocardial perfusion imaging protocol

We performed MPI by a stress-rest imaging protocol with a maximal bicycle test. We started exercise stress testing at 50 Watt, increased by 10 Watt/min, and considered the test optimal when heart rate exceeded 85% of the calculated maximal heart rate (220-age [years]). We recorded symptoms, heart rate, blood pressure, and a 12-lead ECG before, during, and after stress testing. We terminated the exercise stress test if there was physical exhaustion or severe chest pain, >2 mm horizontal or downsloping ST segment depression, >20 mm Hg decrease in systolic blood pressure, or sustained ventricular arrhythmias. We recorded the duration of the stress test, workload (Watt) achieved, and calculated metabolic equivalents (METs = [12 × workload (Watt) + 300] / [weight (kg) × 3.5]). The exercise ECGs were reviewed by a cardiologist with no knowledge of BNP concentrations and >0.1 mV horizontal or downsloping ST segment depression 0.08 seconds after the J-point and/or characteristic symptoms were considered a positive stress test.

We administered 250–350 MBq of technetium-99 m tetrofosmin at peak stress and the patient continued exercise for ≥1 min after the injection to perform MPI. We obtained stress images 45 min after the tracer injection. For rest images, we injected 750–900 MBq 3–4 h after the exercise stress test and obtained images 45 min after tracer injection. We used a two-headed gamma camera (DST-XL, GE Healthcare Technologies) equipped with a low-energy, high-resolution collimator for single photon emission computed tomography with data reconstructed into short axis, vertical long axis and horizontal long axis slices. We used a 17-segment myocardial model for visual perfusion rating with each segment given a score of 0–4 by a specialist in nuclear medicine with no knowledge of BNP concentrations but with access to commercial available software (Quantitative Perfusion Spect, Cedars Sinai, CA, USA). We categorized the patients according to evidence of reversible myocardial ischemia and/or previous myocardial infarction. We calculated left ventricular ejection fraction (LVEF) by the Quantitative Gated Spect software.

2.3. Blood sampling and BNP measurements

We inserted an intravenous line in an antecubital vein and collected blood samples into EDTA tubes before (baseline), immediately after, and 1.5 and 4.5 h after stress testing. We completed blood sample processing within 1 h of collection and the samples were stored at −80 °C and only thawed once before analysis. The SES-BNP assay utilizes a monoclonal capture antibody (Mab 24c5) specific to the ring structure of BNP (sequence $_{11}FGRKMDR_{17}$) and a detection antibody that recognizes the immune complex composed of the capture antibody and BNP (MAb Ab-BNP2) [13], thus the only region of $proBNP_{1-108}$ required for SES-BNP measurement is fragment 11–17 within the ring structure. The characteristics of the SES-BNP assay have been described previously [13]. The lower limit of detection is 0.4 ng/L and the coefficient of variation (CV) of the assay is 9.2% in the lower range (100 ng/L), 9.0% in the intermediate range (1000 ng/L), and 9.2% in the higher range (10000 ng/L).

We also measured BNP by the Siemens ADVIA Centaur BNP sandwich immunoassay (Siemens Healthcare Diagnostics, Erlangen, Germany). The Siemens ADVIA Centaur BNP assay utilizes a capture monoclonal antibody specific to the C-terminus of BNP (BC 203, epitope 27–32) and a detection antibody specific to the ring structure of BNP (KY-hBNP-II, epitope 14–21) [14]. The lower limit of detection of the assay is 2.0 ng/L with a CV of 4.5% in the lower range (45 ng/L) and 4.0% in the higher range (450 ng/L). We analyzed serum creatinine by a standard method and we estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault formula [15]. The laboratory analyses were performed by personnel blinded to clinical information and MPI results.

2.4. Statistical analysis

We present continuous variables as mean (SD) or median (quartile, Q1-3) and categorical variables as absolute numbers and percentages. We assessed normal distribution of continuous variables by the Kolmogorov–Smirnov test. We used the Friedman test to assess whether BNP concentration was similar for the four time points examined, while between group differences at each time point and between time points were compared by the Student's *t*-test and the Mann–Whitney *U* test as appropriate. We compared categorical data by the Chi-square test. We examined factors associated with baseline concentration of the two BNP assays by using backward selection from the full multivariate linear regression models and included age, gender, body mass index (BMI), history of heart failure, CAD, diabetes mellitus, and hypertension, baseline diastolic and systolic blood pressure and heart rate, LV hypertrophy, LVEF, eGFR, evidence of reversible myocardial ischemia and/or previous myocardial infarction

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