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CLINICAL STUDY

N-terminal-proB natriuretic peptide in patients with stable coronary artery disease evaluated for ischemia with myocardial perfusion imaging

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Abstract: Background: Natriuretic peptides have emerged in the last years as useful diagnostic and prognostic biomarkers in patients with stable CAD. Myocardial ischemia per se might increase NT-proBNP levels.
Objectives: The aim of the present study was to determine whether NT-proBNP levels in patients with stable CAD and preserved left ventricular function are elevated and second, to compare NT-proBNP in patients with verified ischemia on myocardial perfusion imaging (MPI) to non-ischemic subjects with known CAD.
Methods: 117 patients were prospectively included, divided in two groups: group A (26 patients) – with normal MPI and without known CAD and group B (91 patients) – with abnormal MPI or known CAD. Patients from group B were further divided according to the presence of ischemia on MPI in non-ischemic (29 pts) and ischemic (62 pts) subgroup.
Results: Levels of NT-proBNP in group B were significantly higher compared to group A (median 53 vs 21pg/ml, p=0.012). End diastolic and end systolic volumes were higher, and ejection fraction after stress and at rest was lower in group B (63 % vs 71 %, p=0.0004 and 69 % vs 75 %, p=0.008). No significant difference in NT-pro BNP levels (median 48 vs 62 pg/ml, p=0.5) and functional parameters between the ischemic and non-ischemic subjects was found.
Conclusion: Our data show that patients with stable coronary artery disease and preserved left ventricular function have elevated levels of NT-proBNP. We could not demonstrate that the presence of myocardial ischemia per se was an additional factor leading to increase of the natriuretic propeptide *(Tab. 4, Ref. 12).* Full Text *(Free, PDF) www.bmj.sk.*
Key words: natriuretic peptide, brain; coronary disease, diagnostic imaging.

Coronary artery disease (CAD) is the most common cardiovascular disease and is the leading cause of mortality in the developed countries. In order to diagnose the disease at its early stages and to improve management and therapeutical approach in patients with already verified CAD, many tests and biomarkers have been introduced.

Brain natriuretic peptide (BNP), a member of the family of natruretic peptides, and his inactive N-terminal propeptide (NT-proBNP) have emerged in the recent years as promising new biomarkers useful in clinical settings for a whole spectrum of patients with CAD. Because of its longer half-life, better stability in-vitro, lower fluctuations and higher plasmatic concentrations compared to BNP, NT-proBNP has found a better acceptance (1).

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Natriuretic peptides have been extensively used in the diagnosis of left ventricular dysfunction, a condition in which their levels are considerably elevated (2). Risk-stratification of patients with acute coronary syndromes is another field where they have been successfully applied (3).

Recently some authors have reported about the diagnostic and prognostic importance of NT-proBNP in stable CAD. Wolber et al. have demonstrated that it could be used as a marker of clinically relevant coronary stenosis and may improve the non-invasive prediction of CAD (4). Ndrepepa et al. have shown that high NT-proBNP levels were linked with highest mortality rate (5).

The objective of our study is to determine whether NT-proBNP levels in patients with stable CAD and preserved left ventricular function are elevated and second, to compare NT-proBNP in patients with verified ischemia on myocardial perfusion imaging (MPI) to non-ischemic subjects with known CAD.

Methods

Patients

In this prospective study 117 patients (67 men, 50 women) with suspected or known CAD were included, referred for myo-

Tab. 1. Basic characteristics of the patients.

Variables	Group A	Group B	p value
No. (%)	26 (22%)	91 (78%)	
Age (y)	56.6±7.5	57±10.2	0.87
Gender (male)	8 (31%)	59 (65%)	0.002
Cardiovascular risk factors			
DM	4 (15%)	25 (27%)	0.21
Hypertension	20 (77%)	63 (68%)	0.41
Smoking	1 (4%)	18 (20%)	0.053
Hyperlipidemia	6 (23%)	36 (39%)	0.13
PVD	1 (4%)	9 (10%)	0.34
Obesity	10 (38.5%)	37 (40%)	0.86
History of CAD	5 (19%)	13 (14%)	0.54
Previous MI	0 (0%)	34 (37%)	
PCI	0 (0%)	27 (29%)	
LBBB	2(8%)	14 (15%)	0.33

DM – diabetes mellitus; PVD – peripheral vascular disease; MI – myocardial infarction; PCI – percutaneous coronary interventions; LBBB – left bundle branch block

Tab. 2. Clinical characteristics of the patients.

Variables	Group A	Group B	p value
Chest pain			
no	5 (19%)	32 (35%)	0.13
typical	2 (8%)	30 (32.5%)	0.01
atypical	19 (73%)	30 (32.5%)	0.0002
CCS class			
1	2 (8%)	24 (26%)	0.047
2	0 (0%)	8 (9%)	0.11
Type of stress			
exercise	15 (58%)	32 (35%)	0.037
dipyridamole	11 (42%)	60 (65%)	0.037

CCS class – Canadian Cardiovascular Society class

cardial perfusion imaging (MPI) to our institution between September 2006 and April 2007.

Criteria for entering the study were suspected CAD or stable CAD class I–III according to Canadian Cardiovascular Society (CCS) ?and preserved left ventricular function at rest (EF > 50 %), measured with gated SPECT. Patients with acute coronary syndromes or severe angina pectoris (CCS class IV), dilated cardiomyopathy, arrhythmia, valvular disease, previous aorto-coronary bypass surgery and renal insufficiency were excluded from the study.

A detailed questionnaire which included clinical, historical and stress data was filled, with particular attention on the risk factors for CAD, previous myocardial infarction (MI) and coronary revascularization.

For the purposes of the study, patients were divided in two groups: *group A* with normal MPI (Summed Stress Score [SSS] ≤1) and not known CAD, and *group B* with abnormal MPI (SSS >1) or already known CAD. Patients from group B were further divided according to the presence of ischemia on MPI in *non-ischemic* (Summed Difference Score [SDS] ≤1) and *ischemic* subgroup (SDS >1).

Myocardial perfusion imaging protocol

One day rest-stress protocol with 99m-Tc sestamibi was performed in all patients. For the rest study 10–12 mCi of the tracer were injected intravenously, in fasting conditions. Imaging started at least 1 hour after radioisotope injection.

Patients able to exercise underwent a symptom-limited exercise treadmill test with the standard Bruce protocol. At near-maximal exercise, radiopharmaceutical (25 mCi) was injected intravenously and exercise was continued at maximal workload for one minute. SPECT acquisition was started 15 to 30 minutes later.

Patients that were unable to exercise from various reasons (e.g. poor conditioning, older age, co morbidity) or could not reach at least 85 % of maximal predicted heart rate, underwent dipyridamole stress. They were instructed not to consume caffeine-containing products for 24 hours before testing.

Dipyridamole infusion in dose of 0.56 mg/kg per body weight for 4 minutes was given and at peak vasodilator effect (3 minutes after the end of the infusion) 25 mCi of the tracer was injected. Two to three minutes later patients with side effects were given aminophyllin as antidote (125 to 250 mg). Results of blood pressure and 12-lead electrocardiograms were recorded at 2-minute intervals. Stress imaging started app. 1 hour after the application of the radiopharmaceutical.

Single photon emission computerized tomography (SPECT)

All patients underwent ECG-synchronized acquisition (gated SPECT) for both studies with rotating single head gamma-camera (Siemens e.cam Signature series). Low energy high resolution (LEHR) collimator was used with step-and-shoot approach for 64 projections over a 180 noncircular orbit around the patients body, beginning at 45 right anterior oblique projection and ending at 45 left posterior. Each projection lasted 25 seconds for the rest and 20 seconds for the stress imaging. ECG-gating was done with 16 frames per cycle.

Image interpretation

Stress and rest images from the short-axis, horizontal long-axis and vertical long-axis slices were compared by four experienced readers, who qualitatively analyzed the images.

Quantitative analysis of the perfusional and functional parameters of the left ventricle during the rest and after stress was done with software package 4D-MSPECT*,* using 17-segments model (6). A summed stress score (SSS) was obtained by means of adding the scores for all segments of the stress images (from 0-normal to 4-absent perfusion for each segment). A summed rest score (SRS) was similarly obtained by means of adding the scores for the same segments of the rest images. The sum of the difference between the stress and rest scores gave summed difference score (SDS).

N-terminal-proB Natriuretic Peptide estimation

Blood samples for NT-proBNP testing were taken from all patients on the day of examination, in the morning. The sera were kept frozen at -20 °C temperature, until the assays were done. NT-proBNP levels in the heparinized plasma were estimated with chemiluminescent immunometric assay (Immulite/ Immulite 1000 *Turbo* NT-proBNP), with analytical sensitivity of 15 pg/ml.

Statistical analysis

Continuous variables were expressed as mean value SD. The mean differences for continuous variables were compared by Student *t* test for parametric data. Mann–Whitney U test was used for nonparametric data and they were expressed as median. Categorical variables were expressed as counts (percentages) and compared by means of a chí square statistic. A p value <0.05 was considered statistically significant.

Results

Patient's characteristics

Basic characteristics of the studied patients are shown on Table 1. No significant differences between the two groups regarding age and cardiovascular risk factors were detected, except for predominant male gender in group B (59/91 vs 8/26, $p=0.002$).

Comparison of the clinical characteristics (Tab. 2) has shown, as expected, significant proportion of patients with typical chest pain and CCS class 1 in group B (32.5 % vs 8 %, $p=0.01$ and 26 % vs 8 %, $p=0.047$ respectively).

Atypical chest pain was more often present in group A, also was the number of patients that underwent exercise stress test (73 % vs 32.5 %, $p=0.0002$ and 58 % vs 35 %, $p=0.037$ respectively).

NT-proBNP and myocardial perfusion scintigraphy findings

NT-proBNP levels in patients with known CAD or abnormal MPI were higher compared to patients without known CAD and normal MPI (160 ± 316 pg/ml vs 55 ± 73 pg/ml, $p=0.02$; $z=-2.275$ with Mann-Whitney U test).

Perfusional and functional parameters of the left ventricle measured with gated SPECT are shown on Table 3. Significant difference between the two groups was found in particular for end diastolic and end systolic volumes and ejection fraction of the left ventricle after stress (91 ± 28.5 ml vs 117 ± 32.7 ml, $p=0.0006$; 28 ± 13.2 ml vs 46 ± 23.2 ml, $p=0.0005$ and 71 ± 6.8 % vs 63 ± 9.2 %, $p=0.0004$ respectively).

Similar results were obtained at resting conditions – end diastolic and end systolic volumes in group B were higher, while ejection fraction was lower (75 ± 7.6 % in group A vs 69 ± 9.8 % in group B, $p=0.008$).

When subjects with myocardial ischemia on MPI were compared with subjects without ischemia and known CAD, no significant difference between NT-pro BNP levels was found. Also there was no difference in functional parameters between the ischemic and non-ischemic group (Tab. 4).

Discussion

Our study has demonstrated that patients with stable coronary artery disease and preserved left ventricular function has increased NT-proBNP levels. These results are in concordance with several other studies (7, 8).

Brain natriuretic peptide (BNP) is a peptide hormone, primarily produced in ventricules as a result of pressure or volumetric stretch of the myocites. Principal pathophysiologic mechanism for its secretion is regional or global systolic or diastolic left ventricular dysfunction, leading consequently to increased wall tension (9). In concordance with this, main clinical use of the natriuretic peptides until recently has been conected with

Tab. 3. NT-proBNP levels and perfusional and functional parameters measured with gated SPECT.

Variables	Group A	Group B	p value
NT-proBNP (pg/ml)	55 ± 73	160±316	
(median)	21	53	0.02
SSS	0.54 ± 0.5	6.6±5.5	0.0000*
SRS	0.27 ± 0.6	4±4.7	0.0001
SDS	0.27 ± 0.4	2.9±2.9	0.0000*
EDV-s (ml)	91 ± 28.5	117±32.7	0.0006
ESV-s (ml)	28 ± 13.2	46±23.2	0.0005
EF-s (%)	71 ± 6.8	63±9.2	0.0004
EDV-r (ml)	89 ± 29.6	110±30.64	0.005
ESV-r (ml)	23 ± 12.7	38±23	0.002
EF-r (%)	75 ± 7.6	69±9.8	0.008

SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; EDV-s – end diastolic volume after stress; ESV-s – end systolic volume after stress; EF-s – ejection fraction after stress; EDV-r – end diastolic volume at rest; ESV-r – end systolic volume at rest; EF-r – ejection fraction at rest; NT-proBNP – N-terminal pro-brain natriuretic peptide

Tab. 4. NT-proBNP levels and gated SPECT parameters in CAD patients with no ischemia and ischemia.

Variables	Group A	Group B	p value
No. (%)	29 (32%)	62 (68%)	
NT-proBNP (pg/ml)	235±469	125±205	
(median)	62	48	0.5
SSS	5±4.8	7±5.8	0.1
SRS	5.5±4.9	3.2±4.6	0.03
SDS	0.34±0.48	4±2.9	0.0000*
EDV-s (ml)	116±30	118±29	0.8
ESV-s (ml)	47±25	45±18	0.76
EF-s (%)	63±9	63±8	0.1
EDV-r (ml)	108±30	111±34	0.7
ESV-r (ml)	41±30	36±17	0.4
EF-r (%)	69±10	69±6	0.1

Abbreviations as in Table 3.

congestive heart failure as an aid in the diagnosis of suspected individuals.

To avoid the influence of left ventricular dysfunction on the results of NT-proBNP in our study, only patients with ejection fraction ≥50 % were included. Comparing the functional parameters of the patients with normal MPI and not known CAD to the group with abnormal MPI or known CAD, the latter had significantly greater end diastolic and systolic volumes and lower ejection fraction, although they were still within the normal limits.

Some authors have reported that increased levels of NT-proBNP are assocciated with myocardial ischemia (10). One of the possible explanations for this observation might be an increase of the left ventricular filling preasure, change that is present relatively early in the course of ischemic cascade and leads to increased wall stress. Additional mechanisms that could also play an important role and might be related to ischemia per se, include upregulation of natriuretic peptides in presence of myocardial hypoxia, what has been shown in experimental studies (11, 12).

In present study, patients with abnormal myocardial perfusion as a whole group, including reversible (ischemic) and fixed perfusional defects, have had increased NT-proBNP. But importantly, NT-proBNP was not significantly different between ischemic and non-ischemic subjects and we have found even higher levels in non-ischemic subgroup. On the other hand, there was no difference in left ventricular volumes and ejection fractions between these two subgroups.

Having all this in mind, we presume that impairment of the functional parameters of the left ventricle was probably the most imortant contributor to the augmentation of NT-proBNP. We could not demonstrate that the presence of myocardial ischemia per se was an additional factor leading to the increase of the B natriuretic propeptide.

We excluded patients with dilated cardiomyopathy, arrhythmia, valvular disease, previous bypass surgery and renal insufficiency in order to avoid potential influence on the levels of NT-proBNP. For these reasons we believe our results are representative, although on limited number of individuals, and they mirror the real status of NT-proBNP in patients with stable CAD.

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