Relation of N-Terminal Pro B-Type Natriuretic Peptide Levels After Symptom-Limited Exercise to Baseline and Ischemia Levels

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Circulating levels of B-type natriuretic peptide (BNP) and the amino-terminal portion of the prohormone (NT-proBNP) have been reported to increase immediately after myocardial ischemia. The association between extent of exercise-induced myocardial ischemia measured using myocardial perfusion scintigraphy and the magnitude and time course of changes in NT-proBNP was studied. One hundred one patients underwent symptom-limited exercise myocardial perfusion scintigraphy. Myocardial ischemia was assessed semiquantitatively. Serum samples were obtained before the start of exercise (baseline), at maximal exercise, and every hour up to 6 hours after maximal exercise. Myocardial ischemia was present in 37 patients (37%). NT-proBNP rapidly increased during exercise (to 113%, interquartile range 104 to 144, and 118%, interquartile range 106 to 142, of baseline, respectively), with a second peak at 4 (141%, interquartile range 119 to 169) and 5 hours (136%, interquartile range 93 to 188), respectively. Absolute changes between NT-proBNP at baseline and at maximum exercise in patients with versus without ischemia were similar (median, 30 pg/ml, interquartile range 7 to 45 vs 15, interquartile range 4 to 46, respectively, $p = 0.230$), but absolute change between baseline and the secondary peak was higher in patients with ischemia than in patients without ischemia (median 64 pg/ml, interquartile range 32 to 172 vs 34, interquartile range 19 to 85, respectively, $p = 0.024$). In multivariate linear stepwise regression analysis of determinants of changes in NT-proBNP after exercise, baseline NT-proBNP was the only independent determinant of absolute changes at maximum exercise, whereas the presence of ischemia was not predictive. Baseline NT-proBNP, cystatin C, and end-systolic volume were independent determinants of the absolute increase to secondary peak levels. In conclusion, myocardial ischemia per se did not lead to additional increases in NT-proBNP within 6 hours after exercise. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:604–610)

B-Type natriuretic peptide (BNP) is a hormone of predominantly ventricular origin that is released into the blood in equimolar portions with its inactive amino-terminal part of the prohormone (NT-proBNP).[1] The diagnostic and prognostic value of NT-proBNP is well established in patients with a variety of clinical conditions, such as heart failure,[2] stable angina pectoris,[3–5] and acute coronary syndromes.[6] Different pathophysiologic mechanisms have been suggested to underlie the increases in circulating BNP and NT-proBNP, such as renal failure,[7] myocyte stretch,[8,9] and myocyte hypoxia.[10] Exercise-induced myocardial ischemia has been reported to induce immediate increases in circulating BNP and NT-proBNP.[11] We hypothesized that immediate and later increases in circulating NT-proBNP occur after exercise-induced myocardial ischemia and that both are associated with the extent of myocardial ischemia. We therefore studied changes in NT-proBNP in patients undergoing symptom-limited exercise myocardial perfusion scintigraphy during a 6-hour observation period after exercise. Second, we studied the potential association of various clinical, biochemical, and scintigraphic variables with the kinetics of NT-proBNP after exercise.

Methods

One hundred one consecutive patients referred for evaluation of the presence or absence of inducible myocardial ischemia and able to perform a bicycle exercise test and subsequent 6-hour blood sampling were included. Patients underwent symptom-limited exercise myocardial perfusion scintigraphy according to a 2-day stress/rest protocol using technetium-99m–tetrofosmin and electrocardiogram (ECG)-gated single-photon emission computed tomography. Blood samples for analysis of NT-proBNP were obtained before the start of exercise, at maximal exercise, and subsequently every hour up to 6 hours after maximal exercise. The local medical ethics committee approved the protocol. All patients gave written informed consent before participation.

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Table 1
Clinical and biochemical characteristics

Characteristics	Overall (n = 101)	Myocardial Ischemia		p Value
		Yes (n = 37)	No (n = 64)	
Men	65 (64%)	30 (81%)	35 (55%)	0.008
Age (yrs)	61 ± 11	61 ± 11	60 ± 11	0.748
Body mass index (kg/m^2)	27 ± 4	27 ± 4	26 ± 4	0.198
Hypertension	45 (45%)	12 (32%)	33 (52%)	0.062
Hypercholesterolemia*	41 (41%)	19 (51%)	22 (34%)	0.094
Current smoking	14 (14%)	5 (14%)	9 (14%)	0.939
Diabetes mellitus	21 (21%)	11 (30%)	16 (25%)	0.605
Documented coronary artery disease†	58 (57%)	29 (78%)	29 (45%)	0.001
Previous myocardial infarction	41 (41%)	24 (65%)	17 (27%)	<0.001
Aspirin use	74 (73%)	31 (84%)	43 (67%)	0.069
Nitrate use	40 (40%)	18 (49%)	22 (34%)	0.158
Calcium antagonist use	31 (31%)	10 (27%)	21 (33%)	0.544
Angiotensin-converting enzyme inhibitor use	28 (28%)	12 (32%)	16 (25%)	0.421
Statin use	48 (48%)	22 (59%)	26 (41%)	0.068
Cystatin C (mg/L)	0.93 (0.83–1.09)	0.92 (0.83–1.12)	0.93 (0.81–1.09)	0.707
Creatinine clearance (ml/min)	95 ± 30	99 ± 31	93 ± 30	0.363
Baseline NT-proBNP (pg/ml)	88 (32–333)	184 (57–386)	74 (21–255)	0.043
Total exercise time (min:s)	8:30 ± 2:32	8:46 ± 2:05	8:21 ± 2:45	0.414
Peak exercise (W)	125 (100–150)	125 (100–150)	125 (100–150)	0.499

Clinical and biochemical characteristics according to presence of myocardial ischemia on the perfusion scan. Values expressed as number (percent), mean ± SD, or median (25th to 75th percentile). Differences between patients with and without myocardial ischemia were assessed using chi-square test, Student's *t* test, and Mann-Whitney rank-sum test, respectively.

* Defined as either serum total cholesterol ≥5.0 mmol/L or use of lipid-lowering medication.

† Defined as previous acute myocardial infarction, history of revascularization (either percutaneous coronary intervention or coronary artery bypass grafting), or documented coronary artery stenosis (>50%) on a coronary angiogram.

Table 2
Myocardial perfusion scintigraphic parameters

Variable	Overall (n = 101)	Ischemia (n = 37)	No Ischemia (n = 64)	p Value
Stress images				
End-diastolic volume (ml)	101 (84–137)	122 (90–179)	93 (80–127)	0.003
End-systolic volume (ml)	43 (29–70)	61 (36–112)	39 (27–60)	0.001
Left ventricular ejection fraction (%)	55 ± 14	48 ± 14	59 ± 12	<0.001
PFR (EDV/s)	1.87 ± 0.53	1.63 ± 0.48	2.01 ± 0.51	<0.001
Time to PFR (ms)	140 (100–190)	130 (100–180)	140 (110–195)	0.297
Stress and rest images SDS	0 (0–4)	6 (4–8)	0 (0–0)	

Values expressed as mean ± SD or median (interquartile range [25th to 75th percentile]). Differences between patients with and without myocardial ischemia were assessed using Student's *t* test and Mann-Whitney rank-sum test, respectively.

EDV = end-diastolic volume.

Myocardial perfusion scintigraphy was performed according to the guidelines of the American Society of Nuclear Cardiology[12] using a 2-day stress/rest protocol. A dose of 500 MBq of technetium-99m–tetrofosmin was administered at rest and at peak exercise. All patients were stressed with a bicycle ergometer with a starting workload of 50 W, increasing every 2 minutes with 25 W. End points for exercise were, among others, achievement of ≥85% of age-predicted heart rate, recognizable chest pain, and >2-mm ST-segment depression.[13] All patients fasted both days, and antianginal medication was discontinued before the exercise test and restarted after exercise. Gated myocardial single-photon emission computed tomography was performed with the patient in a prone position using a 3-headed γ-camera (MultiSPECT-3; Siemens, Hoffman Estate, Illinois). Acquisitions were gated for 16 frames/cardiac cycle. Estimates of left ventricular function (end-diastolic volume, end-systolic volume, and left ventricular ejection fraction) were calculated using a completely automated algorithm, previously described and validated.[14,15] Stress and rest perfusion images were scored in consensus by 2 experienced nuclear medicine