Plasma B-type natriuretic peptide levels are poorly related to the occurrence of ischemia or ventricular arrhythmias during symptom-limited exercise in low-risk patients

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Abstract

Introduction: The usefulness of B-type natriuretic peptide (BNP) as a marker of ischemia is controversial. BNP levels have predicted arrhythmias in various settings, but it is unknown whether they are related to exercise-induced ischemic ventricular arrhythmias.
Material and methods: We analyzed in 63 patients (64 ±14 years, 65% male, 62% with known coronary disease) undergoing exercise stress single-photon emission computed tomography (SPECT) the association between plasma BNP values (before and 15 min after exercise) and the occurrence of ischemia or ventricular arrhythmias during the test.
Results: Exercise test (8.1 ±2.7 min, 7.4 ±8.1 metabolic equivalents, 82 ±12% of maximal predicted heart rate) induced reversible perfusion defects in 23 (36%) patients. Eight (13%) patients presented significant arrhythmias (≥ 7 ventricular premature complexes/min, couplets, or non-sustained ventricular tachycardia during exercise or in the first minute of recovery). Median baseline BNP levels were 17.5 (12.4–66.4) pg/ml in patients developing scintigraphic ischemia and 45.6 (13.2–107.4) pg/ml in those without ischemia ($p = 0.137$). The BNP levels increased after exercise (34.4 (15.3–65.4)% increment over baseline, $p < 0.001$), but the magnitude of this increase was not related to SPECT positivity (35.7 (18.8–65.4)% vs. 27.9 (5.6–64.0)% in patients with and without ischemia, respectively, $p = 0.304$). No significant association was found between BNP values (at baseline or their change during the test) and ventricular arrhythmias.
Conclusions: Plasma BNP values – at baseline or after exercise – were not associated with myocardial ischemia or with ventricular arrhythmia during exercise SPECT. These results highlight the limited usefulness of this biomarker to assess acute ischemia.

Key words: biomarkers, exercise stress test, ischemia, natriuretic peptides.

Introduction

B-type natriuretic peptide (BNP) is secreted in response to myocardial wall stress [1] and has become an established diagnostic and prognos-

tic marker in patients with heart failure [2, 3]. In ischemic heart disease, increased BNP levels have been associated with a worse outcome in patients with ST-elevation acute myocardial infarction [4, 5], non-ST elevation acute coronary syndromes [6], or stable coronary artery disease [7].

Several studies have analyzed the changes in circulating levels of BNP or the amino-terminal portion of the prohormone (NT-proBNP) in response to exercise-induced myocardial ischemia. Whereas some found a direct association between ischemia and the post-ischemic change in BNP levels [8, 9], this association was not observed by others [10]. This issue is clinically relevant since a potentially useful application of BNP could be its measurement as an adjunct to exercise ECG to increase its sensitivity or in the emergency room to help guide management in patients with chest pain of uncertain coronary origin after standard evaluation.

On the other hand, myocardial stretch is arrhythmogenic [11] and wall stress in the ischemic region following coronary occlusion has been related to an increased incidence of ventricular arrhythmias [12–14]. BNP levels have predicted the occurrence of supraventricular or ventricular arrhythmias in various clinical settings [15–17], but their association with ischemic ventricular arrhythmias remains unexplored.

We assessed whether BNP levels are related to the occurrence of ischemia or ventricular arrhythmias during exercise stress test with myocardial perfusion imaging.

Material and methods

Patients

Sixty-three consecutive patients undergoing single-photon emission computed tomography (SPECT) stress testing for diagnostic (n = 24, 38%) or prognostic (n = 39, 62%) purposes were included. Our local Ethics Committee approved the study and all patients provided informed consent. Data were obtained on patients' age, sex, risk factors for coronary artery disease, co-morbidities, previous cardiac disease and ongoing medications.

Ergometry

Patients underwent standard symptom-limited treadmill testing with continuous 12-lead ECG monitoring. If they failed to attain 80% of maximum heart rate in the absence of symptoms or ST-segment depression, an intravenous bolus of dipyridamole was administered at peak exercise [18]. Antianginal medications were not discontinued for prognostic tests. The occurrence of angina or ST-segment changes and the occurrence, number and severity of arrhythmias during exercise and during the first minute of recovery were recorded. Significant ventricular arrhythmia was defined as the occurrence of ≥ 7 premature ventricular premature complexes (VPCs)/min either during exercise or in the recovery phase or the presence of couplets or runs of ventricular tachycardia [19].

Myocardial perfusion imaging

At peak stress, 300 MBq of ^{99m}Tc-tetrofosmin was administered, and imaging was performed immediately afterwards in a dual-head 90° gamma camera (E.CAM, Siemens). Four hours later – 24 h for patients weighing > 90 kg – a second 800 MBq injection was administered and imaging was repeated. A 17-segment myocardial model was used for analysis, with a visual perfusion rating of 0–4 for each segment by two experienced nuclear cardiologists unaware of biomarker data [20]. The difference between stress and rest scores was calculated and scintigraphic ischemia was defined as a summed difference score ≥ 3. Rest gated SPECT was performed and end-systolic and end-diastolic indexed volumes were obtained and ejection fraction calculated [20].

Determination of B-type natriuretic peptide

Venous blood samples were obtained before and 15 min after stress testing. Plasma was stored at –80°C and aliquots were thawed for analysis. A commercially available immunoassay (98000XR, Inverness Medical) was used for measurement of serum BNP.

Statistical analysis

Categorical variables are reported as counts and percentages. Continuous variables are described as mean ± SD or as median (interquartile range) if their distribution follows a non-normal pattern. Comparison between categorical variables was performed by χ^2 tests, and comparison between two continuous variables was performed by Student t-tests or by the Mann-Whitney test for non-normally distributed variables. Paired comparisons involving non-normally distributed variables were performed by the Wilcoxon rank sum test. The Spearman coefficient was used to assess the association between two continuous variables. P-values < 0.05 were considered significant.

Results

Baseline characteristics

Baseline patients' characteristics with regard to the presence or absence of ischemia are shown in Table I. Patients had a significant prevalence of coronary risk factors and of documented ischemic heart disease. The use of antianginal drugs was frequent. Stress-induced myocardial ischemia was

Table I. Clinical characteristics

Parameter	Overall (n = 63)	No ischemia (n = 40)	Ischemia (n = 23)	P-value
Age [years]	64 ±14	64 ±14	63 ±14	0.725
Female gender	22 (35%)	19 (48%)	3 (13%)	0.006
Active smoker	24 (40%)	11 (28%)	13 (65%)	0.005
Diabetes mellitus	17 (28%)	12 (30%)	5 (24%)	0.608
Hypertension	43 (70%)	29 (74%)	14 (64%)	0.378
Dyslipidemia	37 (61%)	22 (56%)	15 (68%)	0.366
Peripheral vasculopathy	5 (8%)	2 (5%)	3 (14%)	0.341
Previous stroke	6 (10%)	4 (10%)	2 (9%)	1.0
Renal insufficiency	5 (8%)	3 (8%)	2 (9%)	1.0
Previous heart failure	5 (8%)	4 (10%)	1 (4%)	0.647
Previous myocardial infarction	20 (34%)	9 (24%)	11 (50%)	0.044
Previous coronary revascularization	27 (44%)	13 (34%)	14 (61%)	0.042
Antiplatelet use	44 (72%)	26 (68%)	18 (82%)	0.205
β-blocker use	27 (44%)	15 (38%)	12 (54%)	0.225
Calcium antagonist use	12 (20%)	8 (20%)	4 (18%)	1.0
Nitrate use	20 (32%)	11 (28%)	9 (39%)	0.374
ACEI/ARB use	33 (54%)	24 (62%)	9 (41%)	0.121
Statin use	35 (57%)	24 (62%)	11 (50%)	0.382

ACEI/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

more frequent in males, in smokers and in those with known coronary artery disease. Echocardiography was available in 29 patients. Three had significant non-coronary heart disease (one obstructive cardiomyopathy, one moderate aortic regurgitation, and one prior arterial switch surgery for transposition of the great arteries) and 9 had non-significant valve disease. Systolic pulmonary artery pressure was calculated in 12 patients; it ranged between 21 mm Hg and 45 mm Hg and was > 30 mm Hg in five.

Exercise stress test and nuclear imaging

The results of the exercise stress test are summarized in Table II. Exercise duration averaged 8.1 ±2.7 min, maximum workload 7.4 ±2.8 metabolic equivalents, and percentage of maximum predicted heart rate 82 ±12%. Nine (14%) patients had angina, which was limiting in 6 (10%). Horizontal or downsloping ST-segment depression appeared in 13 (21%) patients. Five (8%) patients had ≥ 0.2 mV of ST depression during exercise. Reversible perfusion defects were observed in 23 (36%) patients, and 21 (33%) had fixed defects. Mean left ventricular ejection fraction was 57 ±12% and was ≤ 50% in 20 (32%) patients. Of these variables, exercise-induced ischemia was only associated with a greater prevalence of fixed defects.

Ventricular arrhythmias

Twenty-three (36%) patients had ventricular ectopy during exercise. In these patients, the frequency of VPCs was low (2 [1–21]). Four patients (6%) had ≥ 7 VPCs/min during exercise and 4 (6%, 3 of those and 1 additional patient) had ≥ 7 VPCs during the first minute of recovery, 6 (10%) had ventricular couplets and 2 had runs of non-sustained ventricular tachycardia (lasting seven and 18 beats, respectively). Significant arrhythmia, as defined above, was present in 8 (13%) patients, with similar incidence in those with and without ischemia (13% vs. 12%, respectively, p = 1.0).

Plasma B-type natriuretic peptide levels

The BNP values in patients with and without ischemia are illustrated in Table III. The median value of plasma BNP before exercise was 33.7 (12.4–83.0) pg/ml, without differences among patients presenting or not presenting subsequent ischemia. BNP levels increased 15 min after exercise to 51.7 (14.2–96.5) pg/ml (p < 0.001). This

Table II. Exercise stress test characteristics

Parameter	Overall (*n* = 63)	No ischemia (*n* = 40)	Ischemia (*n* = 23)	*P*-value
Total exercise time [min]	8.1 ±2.7	7.9 ±2.4	8.4 ±3.1	0.469
Maximum workload [METS]	7.4 ±2.8	7.3 ±2.8	7.7 ±2.8	0.560
Percentage of maximum predicted heart rate (%)	82 ±12	83 ±12	80 ±11	0.464
Baseline systolic arterial pressure [mm Hg]	131 ±24	133 ±22	128 ±26	0.445
Peak exercise systolic arterial pressure [mm Hg]	157 ±21	158 ±21	155 ±22	0.555
Peak exercise diastolic arterial pressure [mm Hg]	80 ±9	79 ±9	82 ±8	0.162
Exercise-induced angina	9 (14%)	6 (15%)	3 (13%)	1.0
Exercise-induced ST depression 0.1 mV	13 (21%)	8 (20%)	5 (22%)	1.0
Exercise-induced ST depression 0.2 mV	5 (8%)	3 (8%)	2 (9%)	1.0
Myocardial necrosis	21 (33%)	9 (22%)	12 (52%)	0.016
LV end-diastolic volume [ml/m^2]	86 (68–120)	82 (60–102)	94 (76–133)	0.121
LV end-systolic volume [ml/m^2]	38 (25–55)	35 (18–53)	44 (27–73)	0.114
LV ejection fraction (%)	57 ±12	59 ±13	54 ±11	0.093

LV – left ventricle, METS – metabolic equivalents.

Table III. Plasma BNP values in relation to exercise-induced ischemia or significant ventricular arrhythmia

Parameter	Overall (*n* = 63)	No ischemia (*n* = 40)	Ischemia (*n* = 23)	*P*-value	No VA (*n* = 55)	VA (*n* = 8)	*P*-value
Baseline BNP [pg/ml]	33.7 (12.4–83.0)	45.6 (13.2–107.4)	17.5 (12.4–66.4)	0. 137	32.1 (12.2–83.0)	59.4 (19.1–89.1)	0.403
15-min post-exercise BNP [pg/ml]	51.7 (14.2–96.5)	60.4 (17.8–101.4)	28.1 (14.2–85.6)	0.233	46.8 (14.2–94.4)	91.4 (25.8–110.5)	0.269
ΔBNP [pg/ml]	9.3 (1.8–30.0)	10.0 (1.9–31.0)	8.5 (1.8–30.0)	0.937	9.0 (1.8–28.0)	24.8 (2.2–38.8)	0.489
Relative increase in BNP (%)	34.4 (15.3–65.4)	27.9 (5.6–64.0)	35.7 (18.8–65.4)	0.304	34.0 (15.3–66.5)	36.3 (17.3–62.8)	0.901

BNP – type-B natriuretic peptide, VA – ventricular arrhythmia.

increase was of similar magnitude in patients with and without ischemia, whether considered as an absolute increment (Figure 1 A) or as a relative increase over baseline. As compared to the remaining patients (n = 56), those with more severe ischemia (summed difference score ≥ 6, n = 7) also did not have a greater increase in BNP levels after exercise, either absolute (7.4 (1.8–9.0) vs. 10.7 (1.8–32.0) pg/ml, respectively, p = 0.266) or relative (34.4 (25.0–64.3) vs. 35.7 (14.5–66.5) pg/ml, respectively, p = 0.630).

Table III also summarizes BNP values in patients presenting and not presenting arrhythmias. Both groups had similar BNP levels at baseline and after exercise and also had similar absolute (Figure 1 B) or relative increments in BNP levels after exercise with respect to baseline values. The number of VPCs during exercise was not associated with BNP levels at baseline (r = 0.147, p = 0.249) or 15 min after exercise (r = 0.173, p = 0.175) nor with the post-exercise absolute (r = 0.057, p = 0.658) or relative (r = –0.119, p = 0.354) increase in BNP levels with respect to baseline values. The increase in BNP after exercise was not significantly different in the 2 patients presenting runs of non-sustained ventricular tachycardia during the test and in the remaining patients.

As Table IV shows, plasma BNP levels were not associated with other results of exercise SPECT, except for patients with fixed defects having significantly higher baseline BNP levels than those without fixed defects, although the increment in BNP value after exercise was comparable in both groups, and for patients with ≥ 0.2 mV ST depression having a greater relative increase in BNP levels. No significant correlation was found between plasma BNP value at baseline or its absolute increment after exercise and end-diastolic or end-systolic left ventricular volumes or ejection fraction.

Discussion

In the present study, plasma BNP values – at baseline or their increment induced by exercise

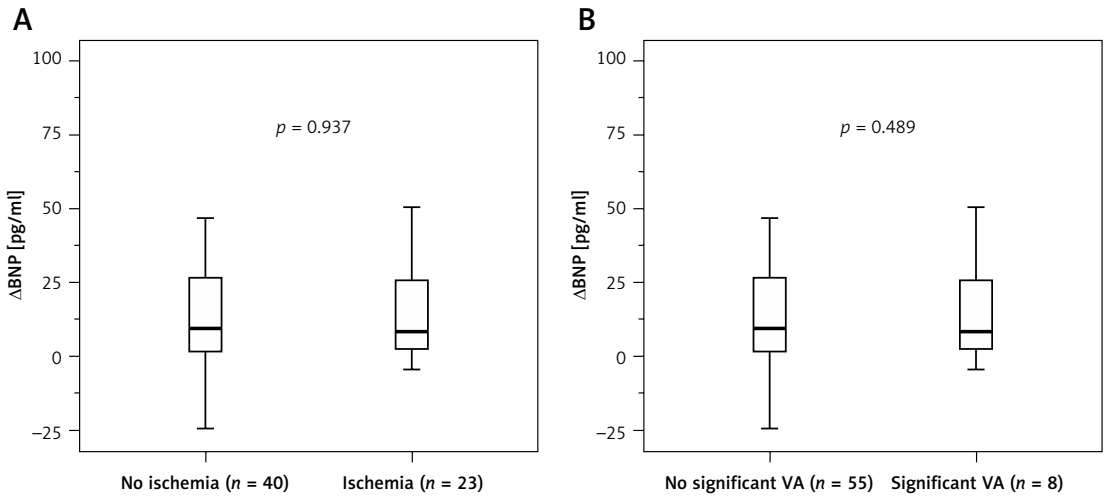

Figure 1. Absolute change in type-B natriuretic peptide levels with regard to the presence or absence of ischemia (**A**) or significant ventricular arrhythmia (**B**) during exercise test (ranges, medians, and 25th to 75th percentiles)

VA – ventricular arrhythmia.

– were not associated with inducible myocardial ischemia or with the occurrence of ventricular arrhythmias during exercise stress SPECT.

Plasma B-type natriuretic peptide levels and exercise-induced ischemia

In part because of their association with depressed ventricular function and/or heart failure, increased BNP or NT-proBNP levels predict a worse outcome across the entire spectrum of ischemic heart disease [4–7]. NT-proBNP has also been shown to contain prognostic information in patients with suspected non-ST-segment elevation acute coronary syndrome [21] and in those arriving in the emergency room with a normal or nearly normal ECG and no troponin elevation [22, 23]. However, BNP and NT-proBNP mainly predict long-term events [21, 23]; it is unclear that they are useful to drive patients' management [24, 25], and their value in the chest pain unit has been challenged when high-sensitive assays are used for troponin detection [26].

Table IV. Plasma BNP values in relation to other results of exercise SPECT

Variable	Baseline BNP [pg/ml]	15-min post-exercise BNP [pg/ml]	ΔBNP [pg/ml]	Relative increase in BNP (%)
Angina:				
No (*n* = 54)	34.5 (12.1–81.7)	54.3 (13.6–98.1)	9.2 (1.8–30.5)	35.8 (14.8–65.7)
Yes (*n* = 9)	24.1 (14.8–116.8)	50.5 (21.4–135.8)	9.4 (2.4–33.0)	24.4 (15.2–48.3)
P-value	0.602	0.716	0.945	0.377
0.1 mV ST depression:				
No (*n* = 50)	32.6 (12.1–83.7)	42.8 (14.0–96.6)	8.4 (1.8–28.0)	27.9 (11.5–61.3)
Yes (*n* = 13)	50.4 (19.9–90.7)	72.1 (28.7–106.8)	21.4 (3.8–42.7)	56.0 (30.0–76.8)
P-value	0.598	0.292	0.122	0.055
0.2 mV ST depression:				
No (*n* = 58)	33.4 (12.4–83.7)	51.1 (14.2–94.9)	8.8 (1.8–28.0)	30.1 (14.3–61.3)
Yes (*n* = 5)	50.4 (13.6–105.2)	89.4 (21.4–181.0)	39.0 (7.8–75.8)	70.1 (52.2–76.8)
P-value	0.815	0.392	0.077	0.021
Fixed perfusion defects:				
No (*n* = 42)	26.0 (9.9–70.2)	35.8 (13.0–93.6)	8.4 (1.8–26.4)	34.7 (15.8–58.6)
Yes (*n* = 21)	66.4 (20.8–99.9)	82.9 (28.2–123.5)	14.4 (2.0–43.4)	28.6 (2.8–69.6)
P-value	0.031	0.052	0.287	0.838

BNP – type-B natriuretic peptide.

In the present study, BNP levels increased shortly after exercise, which concurs with previous observations in healthy people [8, 27] or in patients with suspected or known ischemic heart disease [8–10]. Baseline BNP levels were related to the existence of fixed defects indicating myocardial necrosis. However, neither baseline BNP values nor their increment after exercise were associated with myocardial ischemia. Previous studies that have analyzed the changes in plasma BNP or NT-proBNP in relation to exercise-induced ischemia have obtained conflicting results. Foote *et al.* described in 74 patients with coronary artery disease referred for exercise SPECT that the increment in plasma BNP or NT-proBNP 1 min after exercise was higher in patients with ischemia than in those without ischemia, and suggested that measuring the change in BNPs might be used to increase the sensitivity of exercise ECG for detecting ischemia [8]. Sabatine *et al.* found in 112 patients undergoing exercise SPECT that both baseline BNP values and their increment after exercise were related to the presence and severity of ischemia, this association being less pronounced for NT-proBNP [9]. In contrast, van der Zee *et al.* found in 101 patients undergoing exercise SPECT that, although baseline NT-proBNP values were higher in those subsequently developing ischemia, their increase after exercise was of similar magnitude in patients with and without ischemia [10]. Our results are at variance with those two former studies [8, 9] but, overall, concur with van der Zee's results [10].

The reason for the discrepancy among these otherwise similar studies is unclear. Although differences in populations studied, methodology, results of exercise SPECT or BNP measurement may have played a role, it is likely that the relatively reduced size of the samples and the significant variability of BNP determinations [28] have contributed to these conflicting results. Anyway, the lack of a consistent increase in BNP values associated with acute myocardial ischemia challenges the clinical usefulness of measuring this biomarker during exercise ECG test or in chest pain units. Increased baseline BNP or NT-proBNP levels in patients with inducible myocardial ischemia [9, 10, 29–31] or admitted to the emergency room [32] may just reflect increased wall stress due to impaired systolic and/or diastolic function rather than myocardial ischemia.

Plasma B-type natriuretic peptide levels and ischemic arrhythmias

BNP or NT-proBNP levels have predicted atrial arrhythmias after non-cardiac surgery [15] or after electrical cardioversion [16] and ventricular arrhythmias and sudden death in patients at risk for these arrhythmias [17]. Increased wall stress has been related to ischemic ventricular arrhythmias [12–14], but whether BNP values differ among patients with and without exercise-induced, ischemic arrhythmias is unknown. In the present study, the incidence of ventricular arrhythmias during or after the test was low and comparable to that reported previously [19, 33, 34]. BNP values were not significantly related to the presence or the frequency of VPCs or more complex arrhythmias during exercise, which is not surprising given the rarity of VPCs and arrhythmias and the lack of a significant association between BNP values and ischemia in our series.

Methodological considerations and limitations

The relatively small sample size represents a limitation, particularly for the assessment of the association between BNP levels and arrhythmias. However, the sample size is similar to that of previous studies showing an association between BNP changes and ischemia [8], and the lack of a trend in the association between BNP levels and the occurrence of ischemia or arrhythmias suggest that the results would not have been different with a larger sample size. The limited sample size also made it impossible to explore whether there were differences in BNP values across subgroups of patients with increasing severity of ischemia. Although the results of BNP measurements in the few patients with more severe scintigraphic ischemia argue against this hypothesis, the significantly larger increment in circulating BNP levels in patients with greater exercise-induced ST-segment depression might suggest that severe ischemia could affect BNP levels. Our results cannot be extrapolated to a scenario of prolonged ischemia with significant myocardial injury, where other pathways play a more prominent role [35, 36]. Our patients were all-comers undergoing a SPECT exercise test for diagnostic or prognostic purposes. The results might have been different with more stringent inclusion criteria, but then the clinical relevance would have been lower. BNP values were measured only once after the exercise test, because in previous studies sequential determinations had not provided additional information [9, 10]. Another limitation is that only BNP was analyzed. Combining several biomarkers, particularly high-sensitive troponin [37], or assessing other ECG characteristics exercise [38] might have provided more insight in the study of predictors of ischemia and arrhythmias.

In conclusion, our findings argue against the hypothesis that BNP levels can predict the presence of ischemia and its extension during exercise testing. We also have not found any correlation be-

tween BNP levels and the incidence of arrhythmia during the test. Measuring BNP levels probably has little diagnostic utility in patients undergoing exercise ECG or in those evaluated in the emergency room for suspected acute coronary syndrome.

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Conflict of interest

The authors declare no conflict of interest.

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