B-Type Natriuretic Peptide and Ischemia in Patients With Stable Coronary Disease

Data From the Heart and Soul Study

Kirsten Bibbins-Domingo, PhD, MD; Maria Ansari, MD; Nelson B. Schiller, MD; Barry Massie, MD; Mary A. Whooley, MD

Background—In patients with symptoms of heart failure, elevations in B-type natriuretic peptide (BNP) accurately identify ventricular dysfunction. However, BNP levels are not specific for ventricular dysfunction in patients who do not have overt symptoms of heart failure, suggesting that other cardiac processes such as myocardial ischemia may also cause elevations in BNP.

Methods and Results—To determine whether BNP elevations are associated with myocardial ischemia, we measured plasma BNP levels before performing exercise treadmill testing with stress echocardiography in outpatients with stable coronary disease. Of the 355 participants, 113 (32%) had inducible ischemia. Compared with participants in the lowest BNP quartile (0 to 16.4 pg/mL), those in the highest quartile of BNP (≥105 pg/mL) had double the risk of inducible ischemia (adjusted relative risk, 2.0; 95% CI, 1.2 to 2.6; $P=0.008$). The relation between elevated BNP levels and inducible ischemia was especially evident in the 206 participants who had a history of myocardial infarction (adjusted relative risk, 2.6; 95% CI, 1.5 to 3.7, $P=0.002$) and was absent in those without a history of myocardial infarction (adjusted relative risk, 1.0; 95% CI, 0.3 to 2.2; $P=0.9$). This association between BNP levels and inducible ischemia remained strong after adjustment for measures of systolic and diastolic dysfunction.

Conclusions—Elevated levels of BNP are independently associated with inducible ischemia among outpatients with stable coronary disease, particularly among those with a history of myocardial infarction. The observed association between BNP levels and ischemia may explain why tests for BNP are not specific for ventricular dysfunction among patients with coronary disease. **(*Circulation*. 2003;108:2987-2992.)**

Key Words: natriuretic peptides ■ ischemia ■ myocardial infarction ■ heart failure ■ coronary disease

B-type natriuretic peptide (BNP) is a hormone that is secreted from the cardiac ventricles in response to increased pressure and volume.[1–3] Plasma levels of BNP are increased in patients with ventricular dysfunction and seem to have high sensitivity and specificity for identifying ventricular dysfunction in patients with symptoms of heart failure.[4–9] However, BNP is not an accurate test for ventricular dysfunction among subjects who do not have overt symptoms of heart failure,[10] especially those with underlying coronary disease.[11] These observations suggest that BNP elevations may be associated with cardiac processes other than ventricular dysfunction.

One potential explanation is that elevations of BNP may be the result of ischemia in patients with stable coronary disease. BNP is known to be elevated in acute coronary syndromes and is a powerful predictor of short- and long-term mortality, independent of ventricular function.[12–14] The possibility of an association between BNP and ischemia has been examined only in 3 small studies that have yielded conflicting results.[15–17] To determine whether circulating levels of BNP are associated with inducible ischemia, we measured resting BNP levels and performed exercise echocardiography in 355 patients with stable coronary disease.

Methods

Study Participants

The Heart and Soul Study is a prospective cohort study investigating how psychosocial factors influence the outcomes of patients with coronary disease. We recruited patients with coronary disease who were identified through administrative databases from 2 Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto) and 1 university-based medical center (University of California, San Francisco). Eligible participants had at least 1 of the following: (1) history of myocardial infarction, (2) angiographic evidence of ≥50% stenosis in ≥1 coronary vessels, (3) evidence of exercise-induced ischemia by treadmill ECG or stress nuclear perfusion imaging, (4) a history of coronary revascularization, or (5) a clinical diagnosis of coronary disease as documented by an internist or a cardiologist.

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From the Department of Medicine (K.B.D., M.A., N.B.S., B.M., M.A.W.), Division of Cardiology (M.A., N.B.S., B.M.), and Department of Epidemiology and Biostatistics (M.A.W.), University of California, San Francisco; the VA Medical Center (M.A., N.B.S., B.M., M.A.W.), San Francisco; and University of California, San Francisco.

Correspondence to Mary A. Whooley, MD, 4150 Clement St (111A1), San Francisco, CA 94121. E-mail whooley@itsa.ucsf.edu

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All eligible patients were invited by mail to attend a baseline study appointment, and a total of 510 participants enrolled between September 2000 and December 2001. Patients were excluded if they were unable to walk 1 block or were planning to move out of the local area within 3 years. For this cross-sectional study, we excluded 4 participants who had inadequate echocardiographic data and 151 for whom we could not obtain a blood sample after the 30-minute rest period (because of dislodged or thrombosed butterfly needle), leaving a total of 355 participants for the analysis. The institutional review board at each of the sites described above approved this protocol. All participants provided written informed consent.

Measurements

B-Type Natriuretic Peptide

Before the study appointment, participants completed an overnight fast except for taking their regularly prescribed medications. A 21-gauge butterfly needle was inserted intravenously in the forearm, and after a 30-minute supine rest, blood samples were drawn into chilled EDTA tubes, mixed with aprotinin, then divided into aliquots and stored at −70°C for up to 9 months. We used the Triage B-type natriuretic fluorescence immunoassay (Biosite Diagnostics) to measure BNP in frozen plasma samples thawed to room temperature. The lowest detectable measurement for this assay was 5 pg/mL. The interassay coefficient of variation was 10.1% for 28.8 pg/mL, 12.4% for 586 pg/mL, and 16.2% for 1180 pg/mL. The laboratory technician who measured BNP was at a different site and blinded to the characteristics of the patients and the results of the echocardiograms and stress tests.

Ischemia

After plasma was drawn and frozen for measurement of BNP, all participants underwent full exercise treadmill testing according to a standard Bruce protocol with continuous 12-lead ECG monitoring. An echocardiogram was performed immediately before and after exercise with an Acuson Sequoia Ultrasound System with a 3.5-MHz transducer. Inducible ischemia was defined as the presence of ≥1 new wall motion abnormalities at peak exercise. One of us (N.B.S.) interpreted all of the echocardiograms, blinded to the results of the BNP assay, the resting echocardiogram, and the clinical history.

Other Measurements

A complete resting 2D echocardiogram and Doppler ultrasound examination, including all standard views and subcostal imaging of the inferior vena cava, was performed. We obtained standard 2D parasternal short-axis and apical 2- and 4-chamber views during held inspiration; these were planimetered with a computerized digitization system to determine end-diastolic and end-systolic left ventricular volume. We calculated left ventricular ejection fraction (LVEF) as (end-diastolic volume−end-systolic volume)/end-diastolic volume. We defined 3 categories of diastolic dysfunction by peak early diastolic filling velocity (E velocity) and peak filling velocity at atrial contraction (A velocity): (1) impaired relaxation=E/A ratio <1.0 and systolic-dominant pulmonary vein flow, (2) pseudonormal=E/A ratio ≥1 and <2 and diastolic-dominant pulmonary vein flow, and (3) restrictive filling=E/A ratio ≥2 and diastolic-dominant pulmonary vein flow.[18] Left ventricular hypertrophy was defined as left ventricular mass index >90 g/m^2.

To account for ventricular dysfunction that might be manifest during exercise, we measured postexercise LVEF and wall motion score index. Postexercise LVEF was assessed immediately after exercise. We calculated a wall motion score index at peak exercise using the following method. Each of 16 wall segments in the left ventricle was scored on the basis of the contractility visualized at peak exercise (1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic, 5=aneurysm, 0=not visualized). The wall motion score index was defined as the sum of wall motion scores divided by the number of segments visualized, with a normally contracting left ventricle receiving a wall motion score index of 1 (16/16=1) and higher wall motion scores indicating worse contractility.[19]

Age, sex, race/ethnicity, medical history, and smoking status were determined by patient questionnaire. Alcohol use was measured by use of the AUDIT-C questionnaire, with a score of ≥4 used to define regular alcohol use. We measured weight and height and calculated body mass index (kg/m^2). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Total cholesterol, HDL cholesterol, and LDL cholesterol levels were measured from sera after the overnight fast. We calculated creatinine clearance from 24-hour urine collections.

Analysis

We divided participants into quartiles on the basis of their plasma BNP levels. Differences in characteristics across quartiles were compared by ANOVA (or nonparametric equivalent) for continuous variables and χ^2 tests for dichotomous variables. We compared median BNP values for various degrees of inducible ischemia using a Kruskal-Wallis rank test. To determine the independent association between BNP and inducible ischemia, we used logistic regression analyses with quartiles of BNP as the primary predictor and inducible ischemia as the outcome. To obtain adjusted risk estimates, we entered all variables, including quartiles of BNP, into a backward stepwise elimination model. Variables associated with inducible ischemia at $P<0.1$ were retained in the final model. Because BNP is known to be associated with systolic and diastolic dysfunction,[5,6] we also examined the association between BNP and inducible ischemia with LVEF and diastolic dysfunction forced into the models. We converted odds ratios and 95% CIs from the multivariate logistic regression models into relative risks.[20]

We tested for interactions between the highest quartile of BNP (compared with the lowest) and history of myocardial infarction, history of coronary revascularization, left ventricular hypertrophy, LVEF, diastolic dysfunction, and use of cardiac medications. We performed analysis stratified by any variables with $P<0.1$ for interaction. All analyses were performed with Stata statistical software, version 7 (1996).

Results

The median BNP level in our sample was 36.6 pg/mL (interquartile range, 16.4 to 104 pg/mL). Compared with participants in the lowest quartile of BNP, those in the highest quartile were older, more likely to be white, and more likely to have left ventricular hypertrophy, lower LVEF, or diastolic dysfunction. They had lower exercise capacity, lower total and LDL cholesterol, and lower creatinine clearance. Participants in the highest quartile of BNP were more likely to be taking β-blockers, renin-angiotensin inhibitors, or diuretics than those in the lowest quartile (Table 1).

Of the 355 participants, 113 (32%) had inducible ischemia. Plasma BNP levels ranged from 30.8 pg/mL (interquartile range, 14.4 to 73.9 pg/mL) in the 242 participants without evidence of exercise-induced ischemia to 48.7 pg/mL (interquartile range, 20.5 to 131 pg/mL) in the 79 participants with 1 exercise-induced wall motion abnormality to 71.7 pg/mL (interquartile range 20.5 to 131) in the 34 participants with >1 exercise-induced wall motion abnormality ($P<0.001$).

The proportion of participants with inducible ischemia increased by quartile of BNP (Figure). Forty-six percent of participants in the highest quartile of BNP had inducible ischemia compared with 20% in the lowest quartile (unadjusted relative risk, 2.3; 95% CI, 1.6 to 3.2; $P<0.001$). After adjusting for potential confounders, we found that participants in the highest quartile of BNP had double the risk of inducible ischemia compared with those in the lowest quartile (Table 2). Because ventricular systolic and diastolic dysfunction is a potential mediator of the association between BNP

TABLE 1. Characteristics of 355 Participants With Stable Coronary Disease by Quartile of B-Type Natriuretic Peptide*

	Quartile of B-Type Natriuretic Peptide, pg/mL				
	I (0–16.4)	II (16.5–36.6)	III (37.0–104)	IV (105–636)	*P*
Age, y	63±12	68±9	71±10	75±8	<0.001
Male sex, %	90	92	92	95	0.60
White race/ethnicity, %	50	68	69	71	0.01
Hypertension, %	62	72	65	76	0.19
Chronic obstructive pulmonary disease, %	20	16	18	11	0.36
Diabetes, %	25	25	20	33	0.28
Previous myocardial infarction, %	55	53	62	64	0.41
Previous stroke, %	8	14	18	17	0.21
Previous revascularization, %	64	68	65	71	0.77
Current smoking, %	21	18	11	9	0.08
Regular alcohol consumption, %	27	36	24	31	0.31
Left ventricular hypertrophy, %	4	10	3	24	<0.001
LVEF	0.64±0.9	0.64±0.9	0.63±0.9	0.58±0.12	<0.001
Diastolic dysfunction, %					<0.001
Impaired relaxation	62	61	51	40	
Pseudonormal	3	8	11	13	
Restrictive	0	0	7	16	
Body mass index, kg/m^2	29±6	28±4	28±4	28±5	0.31
Exercise capacity, METS	8.5±3.7	7.9±2.9	7.2±3.5	5.4±2.6	<0.001
Total cholesterol, mg/dL	187±42	175±39	180±44	168±40	0.02
LDL cholesterol, mg/dL	110±33	102±32	102±30	97±31	0.05
HDL cholesterol, mg/dL	48±13	46±14	47±17	44±13	0.38
Creatinine clearance, mL/min	94±28	81±26	79±26	64±25	<0.001
Current β-blocker use, %	42	60	67	69	0.001
Current renin-angiotensin inhibitor use, %	39	51	48	66	0.004
Current diuretic use, %	22	23	29	43	0.008
Current aspirin use, %	76	94	78	81	0.005
Current statin use, %	61	78	74	70	0.07

*Plus-minus values are mean±SD.

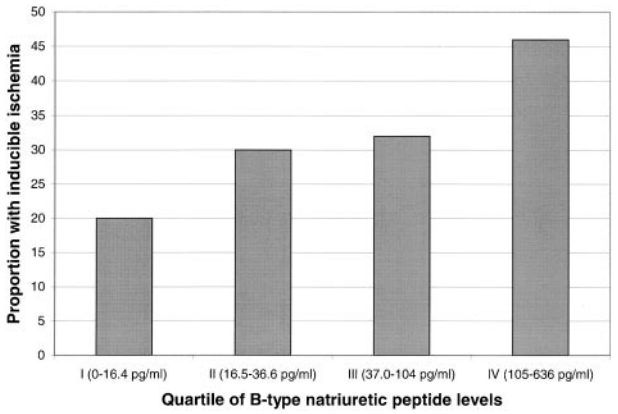
and inducible ischemia, we evaluated the association of the highest quartile of BNP with inducible ischemia after adjustment for ventricular dysfunction. We found that the risk for inducible ischemia associated with the highest quartile of BNP remained present even after control for both systolic and diastolic dysfunction (Table 3).

We found no evidence for interaction between BNP and history of revascularization, left ventricular hypertrophy, LVEF, diastolic dysfunction, or use of renin-angiotensin inhibitors, β-blockers, diuretics, statins, or aspirin (all probability values >0.10). However, the association between BNP and inducible ischemia varied by history of myocardial

TABLE 2. Association Between B-Type Natriuretic Peptide and Inducible Ischemia in 355 Participants With Coronary Disease

B-Type Natriuretic Peptide, pg/mL	No. (%) With Inducible Ischemia	Adjusted Relative Risk* (95% CI)	*P*
Quartile I (0–16.4)	18/90 (20)	1.0	...
Quartile II (16.5–36.6)	26/88 (30)	1.4 (0.7–2.1)	0.29
Quartile III (37.0–104.0)	29/91 (32)	1.5 (0.8–2.3)	0.14
Quartile IV (105–636)	40/86 (46)	2.0 (1.2–2.8)	0.008

*All variables from Table 1 were entered into backward elimination logistic regression models including B-type natriuretic peptide. The other variables associated with inducible ischemia (at $P<0.1$) were exercise capacity and aspirin use.



Proportion of participants with inducible ischemia by quartile of BNP (probability value from $\chi^2=0.002$).

infarction (*P* for interaction=0.05). We observed an association between BNP and ischemia among the 206 participants who reported a history of myocardial infarction but not among the 147 participants without a history of myocardial infarction (Table 4). Elevated BNP remained strongly associated with inducible ischemia among participants with a history of myocardial infarction even after exclusion of the 48 participants with LVEF <55%.

To explore potential mediators between BNP and inducible ischemia among participants with a previous myocardial infarction, we further adjusted for LVEF after exercise and wall motion score index measured at peak exercise. The association between BNP and inducible ischemia was present even after adjustment for these measures of inducible ventricular dysfunction (Table 5).

TABLE 3. Association of Highest Quartile of B-Type Natriuretic Peptide With Inducible Ischemia After Adjustment for Ventricular Dysfunction

	Adjusted Relative Risk (95% CI)*	*P*
Baseline model	2.0 (1.2–2.8)	0.008
Adjusted for LVEF	1.9 (1.2–2.8)	0.01
Adjusted for categories of diastolic dysfunction	1.8 (1.1–2.7)	0.02
Adjusted for both LVEF and categories of diastolic dysfunction	1.8 (1.0–2.7)	0.04

*Adjusted for exercise capacity and aspirin use.

Discussion

We found that BNP was associated with inducible ischemia among patients with stable coronary disease. This association was seen most strongly among participants with a history of myocardial infarction and was independent of systolic and diastolic dysfunction. The association we observed between elevated BNP and inducible ischemia may explain why elevations in BNP are not specific for detecting asymptomatic ventricular dysfunction in patients with coronary disease. Our findings also offer a potential explanation for the increased risk of future coronary events associated with BNP elevations after acute coronary syndromes,[12–14] although the causal pathway between BNP and inducible ischemia cannot be determined by this cross-sectional study.

Three previous studies have examined the association between BNP and inducible ischemia. One found higher resting BNP levels in 19 subjects with ischemia compared with 12 subjects without inducible ischemia, but this study was restricted to patients with hypertrophic cardiomyopathy,

TABLE 4. Association Between Quartiles of B-Type Natriuretic Peptide and Inducible Ischemia, Stratified by History of Myocardial Infarction

BNP Quartile	No. (%) With Inducible Ischemia	Adjusted Relative Risk* (95%CI)	*P*
Participants without history of myocardial infarction (n=147)†			
I	9/40 (22)	1.0	...
II	13/41(32)	1.2 (0.5–2.5)	0.57
III	8/35 (23)	0.7 (0.2–1.9)	0.61
IV	11/31 (31)	1.0 (0.3–2.2)	0.9
Participants with history of myocardial infarction (n=206)†			
I	9/48 (19)	1.0	...
II	13/47 (28)	1.4 (0.6–2.6)	0.37
III	21/56 (38)	1.9 (1.0–3.1)	0.04
IV	29/55 (53)	2.6 (1.5–3.7)	0.002
Participants with history of myocardial infarction and LVEF >55% (n=158)			
I	6/34 (18)	1.0	...
II	10/38 (26)	1.4 (0.6–2.8)	0.40
III	14/49 (29)	1.6 (0.6–2.8)	0.29
IV	23/37 (62)	3.1 (1.8–4.2)	0.001

*Relative risk of inducible ischemia adjusted for exercise capacity and aspirin use.
†Includes participants with both normal and depressed systolic function.

TABLE 5. Association Between B-Type Natriuretic Peptide and Inducible Ischemia in Participants With History of Myocardial Infarction, Adjusted for Potential Mediators

	Participants With History of Myocardial Infarction		Participants With History of Myocardial Infarction and LVEF >55%	
	Adjusted Relative Risk* (95% CI)	*P*	Adjusted Relative Risk† (95% CI)	*P*
Baseline model	2.6 (1.5–3.7)	0.002	3.1 (1.8–4.2)	0.001
Adjusted for postexercise LVEF	2.0 (1.0–3.2)	0.05	2.8 (1.4–4.0)	0.005
Adjusted for wall motion score index	2.1 (1.0–3.3)	0.06	2.6 (0.8–4.3)	0.08
Adjusted for postexercise LVEF and wall motion score index	2.2 (1.0–3.5)	0.04	2.6 (0.8–4.3)	0.09

*Comparing 55 participants in the highest BNP quartile with 48 participants in the lowest BNP quartile. All models adjusted for exercise capacity and aspirin use.

†Comparing 37 participants in the highest BNP quartile with 34 participants in the lowest BNP quartile. All models adjusted for exercise capacity and aspirin use.

so its clinical implications are unclear.[15] A second study found no difference in resting BNP levels between 10 patients with stable angina and 15 control subjects.[17] However, a third study of 35 patients with known angina found that BNP levels increased after exercise. Indeed, the degree of BNP elevation corresponded with the size of ischemic territory, suggesting that inducible ischemia may lead to elevations in BNP.[16]

Our study found an association between resting BNP and ischemia in a large sample of outpatients with stable coronary disease. These results suggest that study participants who had inducible ischemia were probably also experiencing ischemia in their daily lives.[21] Such daily ischemia may cause increased ventricular volume and wall stress, leading to elevations in BNP. Alternatively, it is possible that elevations in BNP are part of a process leading to ischemia, with elevated BNP reflecting increased ventricular filling pressures that may lead to increased demand and greater myocardial ischemia.

In stratified analyses, we observed the strongest association between BNP and inducible ischemia among participants with a previous myocardial infarction. These results suggest that participants with a history of myocardial infarction may be more likely to develop elevated filling pressures in response to ischemia, perhaps because of previous myocardial damage. Alternatively, previous myocardial damage may make participants with a history of myocardial infarction more likely to develop ischemia in response to increased volume and filling pressures. Finally, it is possible that myocardial infarction is simply an initial trigger for the release of BNP, as has been observed in other settings.[22–25]

The elevation of BNP in outpatients with inducible ischemia has implications for the use of BNP as a diagnostic test for systolic dysfunction. Many (including the European Society of Cardiology) have proposed that BNP should be used as a first-line test for patients with symptoms suggestive of ventricular dysfunction, particularly high-risk patients such as those with coronary disease.[26,27] Our finding that BNP levels are elevated in patients with inducible ischemia independent of ventricular dysfunction suggests that symptomatic patients with BNP elevations may need further evaluation with ischemia testing, in addition to assessment of ventricular function, particularly because distinguishing symptoms of chronic ischemia from those of ventricular dysfunction can be problematic.

Several limitations should be considered in interpreting our results. First, we are unable to determine the causal pathway between BNP and ischemia because of the nature of our cross-sectional study design. Second, although we chose a common definition for diastolic dysfunction[18] and found that diastolic dysfunction did not mediate the association between BNP and ischemia, definitions of diastolic dysfunction are the subject of much debate. Thus, we cannot exclude the possibility that other definitions might reveal diastolic dysfunction as a mediator of this association. Finally, BNP levels may vary by sex,[28] and given the predominantly male population, our study does not allow for an assessment of the association between BNP and inducible ischemia in women.

In summary, we found that BNP is associated with inducible ischemia among patients with stable coronary disease and that this association is strongest among those with a history of myocardial infarction. The association we observed between BNP and ischemia suggests a potential explanation for the increased risk of future coronary events associated with elevations in BNP and may also explain why BNP is not an accurate screening test for ventricular dysfunction in patients with stable coronary disease.

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