The Effect of Diabetes on B-Type Natriuretic Peptide Concentrations in Patients With Acute Dyspnea

An analysis from the Breathing Not Properly Multinational Study

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OBJECTIVE — Diabetes has been implicated in reduced myocardial compliance and changes in the intercellular matrix of the myocardium. We determined the effect of diabetes on B-type natriuretic peptide (BNP) concentrations in patients presenting to the emergency department with dyspnea.

RESEARCH DESIGN AND METHODS — The Breathing Not Properly Multinational Study was a prospective evaluation of 1,586 patients. A subset of 922 patients was obtained and subdivided into the following groups: group 1 (n = 324), neither diabetes nor heart failure; group 2 (n = 107), diabetes and no heart failure; group 3 (n = 247), no diabetes and heart failure; group 4 (n = 183), both diabetes and heart failure; group 5 (n = 41), heart failure history with no diabetes; and group 6 (n = 20), heart failure history with diabetes. Patients from groups 1, 3, and 5 were matched to groups 2, 4, and 6, respectively, to have the same mean age, sex distribution, BMI, renal function, and New York Heart Association (NYHA) classification (for heart failure).

RESULTS — There was no significant difference in median BNP levels between diabetes and no diabetes among no heart failure patients (32.4 vs.32.9 pg/ml), heart failure patients (587 vs. 494 pg/ml), and those with a heart failure history (180 vs. 120 pg/ml). Receiver-operating characteristic curve analysis of the area under the curve for BNP was not different in diabetic versus nondiabetic patients (0.888 vs. 0.878, respectively). However, in a multivariate model, diabetes was an independent predictor of a final diagnosis of heart failure (odds ratio 1.51, 95% CI 1.03–2.02; $P < 0.05$).

CONCLUSIONS — History of diabetes does not impact BNP levels measured in patients with acute dyspnea in the emergency department. Despite the impact of diabetes on the cardiovascular system, diabetes does not appear to confound BNP levels in the emergency department diagnosis of heart failure.

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Cardiovascular disease, including coronary heart disease and cerebrovascular disease, is the leading cause of morbidity and mortality in patients with type 1 and 2 diabetes (1). Diabetic patients are also at increased risk for congestive heart failure. The Framingham Heart Study (2) showed that incidence of heart failure for diabetic men was twofold higher than that for nondiabetic people and fivefold higher for diabetic versus nondiabetic women. Patients with diabetic cardiomyopathy have clinical and anatomic features of heart failure that are different from other heart failure patients (3). The left ventricular remodeling results from a combination of activation of the sympathetic nervous system and renin-angiotensin system, hypertension, hyperglycemia, and insulin resistance (4). Diabetic cardiomyopathy develops independent of the presence of ischemic heart disease or valvular or congenital heart disease (5).

B-type natriuretic peptide (BNP) is a

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Abbreviations: AUC, area under the curve; BNP, B-type natriuretic peptide; CIE, clinical indication for echocardiography; NYHA, New York Heart Association; ROC, receiver-operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

biomarker that is released into the blood in response to ventricular stretching, volume overload, and increased wall tension (6). Assays for BNP are approved for use as an aid in the diagnosis of heart failure for patients who present with dyspnea. Clinical trials are underway to determine whether serial BNP testing can be used to monitor the success of drug therapy given to heart failure patients, which has been demonstrated in pilot studies (7). The use of BNP for screening asymptomatic subjects for heart failure is controversial. It may be possible that testing high-risk groups, such as those with diabetes, may improve the efficacy of screening programs for BNP (8). In a recent study (9) of diabetic patients at a Veterans Administration hospital, BNP was found to reliably screen for the presence or absence of left ventricular dysfunction.

In this study, we examined data from the Breathing Not Properly Multinational Trial to determine whether BNP concentrations are different for diabetic versus nondiabetic patients who present at the emergency department with acute dyspnea.

RESEARCH DESIGN AND METHODS

— The Breathing Not Properly Multicenter Study was an international, seven-center, prospective study (five U.S. centers and two European centers). The study design and main results of the Breathing Not Properly Multinational Study have been published elsewhere (10). Study investigators and centers are listed in the APPENDIX. The study was conducted from April 1999 to December 2000. The study protocol was approved by the institutional review boards of all study centers, and written informed consent was obtained from all participants.

A total of 1,666 patients presenting to the study centers with a primary complaint of dyspnea were screened. Eighty patients were excluded from the study based on the protocol exclusion criteria, which included the presence of advanced renal failure (on dialysis or estimated glomerular filtration rate of <15 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}) (11), acute myocardial infarction, or overt cause of dyspnea including chest wall trauma or penetrating lung injury. A final total of 1,586 participants were enrolled in the study. There were 367 patients (23.1%) who had diabetes listed in the final discharge diagnosis and 1,219 (76.9%) who did not.

Data collection

Baseline demographics, clinical history, and objective assessment of clinical signs were gathered by trained research personnel in the emergency department, including age, sex, race, height, and weight (necessary for calculation of BMI). Findings from the electrocardiogram, chest X-ray, and blood tests, including serum creatinine, were recorded in a structured checklist completed by the emergency department attending physician. From the database of 1,586 patients, subgroups were prepared based on the presence of diabetes and heart failure status (active versus having history of dyspnea, but not due to heart failure). Because BNP concentrations in healthy individuals are dependent on age, sex, BMI, renal function (12), and New York Heart Association (NYHA) classification (for heart failure patients), a subset of data were prepared whereby these parameters were matched between the no heart failure, heart failure, and history of heart failure groups (but not active heart failure). The database was sorted according to BMI and sex, given that these parameters were the most different between the diabetic and nondiabetic groups. Lean nondiabetic female patients were consecutively removed from the nondiabetic groups until the BMI and sex matched the diabetic group. Retrospectively, no adjustments in the database were necessary for the estimated creatinine clearance. After all adjustments, the final subgroupings were: group 1 ($n = 324$) had neither diabetes nor heart failure, group 2 ($n = 107$) had diabetes and no heart failure, group 3 ($n = 247$) had heart failure but not diabetes, group 4 ($n = 183$) had both diabetes and heart failure, group 5 had a history of heart failure but current dyspnea not due to heart failure and no diabetes ($n = 41$), and group 6 ($n = 21$) had a history of heart failure and diabetes.

Measurement of BNP

During initial evaluations, 5 ml of blood was collected into tubes containing K_3EDTA, and the BNP concentration was measured using the first generation Triage B-Type Natriuretic Peptide test (Biosite, San Diego, CA). Precision, analytical sensitivity, and stability characteristics of the system have been previously described (13). The measurable range of the BNP assay was 5.0–1,300 pg/ml. (After completion of this study, the manufacturer has released a second-generation BNP assay whereby the assay range has been extended to 5,000 pg/ml.) The test was run in a concealed fashion, with the results kept in separated data binders only linked by a separate study code, hence blinding both emergency department physicians and adjudicating cardiologists.

Reference standard definition for heart failure

Approximately 30 days after the emergency department visit, the case report form (excluding the emergency department physician estimate of probability of heart failure), electrocardiogram, chest X-ray, echocardiogram, and all other clinical tests, consultations, and chart information were reviewed by two independent cardiologists. In addition, information was used from the case report form to calculate the Framingham (requiring two major or one major and two minor criteria for heart failure) and National Health and Nutrition Examination Survey (requiring three or more points for heart failure) scores for heart failure. After reviewing all information, if agreement was achieved, then the case was categorized as one of the following: *1*) dyspnea due to heart failure, *2*) history of heart failure but dyspnea due to noncardiac cause, or *3*) dyspnea due to noncardiac cause. In the event of disagreement, the case was adjudicated by the study end points committee.

Statistical analysis

Baseline characteristics were reported in counts and proportions or means ± SDs as appropriate. Univariate comparisons of the nonparametric data were made with the Wilcoxon test using the median and 95% CIs. A P value of <0.05 was considered significant. Separate receiver-operating characteristic (ROC) curves were generated for BNP and the final diagnosis of heart failure in diabetic versus all subjects. The area under the ROC curve (AUC) and 95% CIs were reported. Multiple conditional logistic regression was used to evaluate the independent relationships between clinical factors including BNP and presence or absence of diabetes on the outcome of final adjudicated diagnosis of heart failure. Statistical calculations were performed using MedCalc for Windows version 7.3.0.1 (Berkeley, CA).

RESULTS

— Table 1 illustrates the baseline characteristics of the entire

Table 1—*Baseline characteristics of the diabetic and nondiabetic groups (all subjects)*

	Diabetic	Nondiabetic	*P*
n	367 (23.1)	1,219 (76.9)	—
Demographics			
Age (years)	65.6 ± 13.02	63.5 ± 17.6	0.04
Men	218 (59.4)	665 (45.4)	NS
Caucasian	169 (46.0)	604 (46.0)	NS
African American	179 (48.8)	536 (44.0)	NS
Other race	19 (5.2)	79 (6.5)	NS
BMI (kg/m^2)	31.6 ± 8.4	27.9 ± 8.3	<0.0001
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	63.0 ± 36.8	65.8 ± 33.0	NS
Medical history			
Hypertension	280 (76.3)	599 (49.1)	<0.001
COPD or asthma	123 (33.5)	477 (39.1)	0.05
Atrial fibrillation	66 (18.0)	190 (15.6)	NS
Stable angina	100 (27.2)	208 (17.1)	<0.001
Prior myocardial infarction	120 (32.7)	265 (21.7)	<0.001
Prior CABG	68 (18.5)	108 (8.9)	<0.001
Prior heart failure	165 (45.0)	362 (29.7)	<0.001
Chronic medications			
ACE inhibitors	164 (44.7)	321 (26.3)	<0.001
β-Blockers	93 (25.3)	249 (20.4)	0.05
Calcium channel blockers	108 (29.4)	222 (18.2)	<0.001
Antiarrhythmics	34 (9.3)	71 (5.8)	0.02
Diuretics	227 (61.9)	515 (42.2)	<0.001
Digoxin	84 (22.9)	209 (17.1)	0.01
Symptoms			
Paroxysmal nocturnal dyspnea	234 (63.8)	626 (51.4)	<0.0001
Orthopnea	238 (64.9)	672 (55.1)	0.001
Night cough	155 (42.2)	531 (43.6)	NS
Fatigue or weakness	272 (74.1)	874 (71.7)	NS
Heart rate (bpm)	91 ± 23	93 ± 23	NS
Systolic blood pressure (mmHg)	141 ± 31	141 ± 30	NS
Diastolic blood pressure (mmHg)	77 ± 20	80 ± 18	0.006
Elevated jugular venous pressure	106 (28.9)	276 (43.2)	0.01
Rales (any lung field)	192 (52.3)	527 (43.2)	0.002
Enlarged PMI	46 (12.5)	130 (10.7)	NS
S3	30 (8.2)	103 (8.4)	NS
Hepatomegaly or HJR	47 (12.8)	165 (13.5)	NS
Edema	206 (56.1)	478 (39.2)	<0.0001

Data are *n* (%) or means ± SD. CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HJR, hepatojugular reflux; PMI, perioperative myocardial infarction.

1,586-patient dataset, comparing the 367 patients with diabetes with the 1,219 patients without diabetes. Diabetic patients were slightly older (65.6 vs. 63.5 years), had a more frequent history of heart disease (stable angina, prior myocardial infarction, prior coronary artery bypass graft surgery, heart failure, higher diastolic blood pressure, elevated jugular venous pressure, orthopnea, and paroxysmal nocturnal dyspnea), and therefore a higher incidence of cardiac medications (ACE inhibitors, β-blockers, calcium channel blockers, antiarrhythmics, diuretics, and digoxin). They also had a higher mean BMI (31.6 vs. 27.9 m/kg^2). Estimated creatinine clearance was lower for the diabetic group (65.8 vs. 63.0 ml · min^{-1} · 1.73m^{-2}), but results were not statistically different.

Correlation between BNP and presence of diabetes

Table 2 illustrates the results of the subgroup analysis that were matched for median age, sex, BMI, estimated creatinine clearance, and NYHA classification (for heart failure patients). With regard to average BNP concentrations, there was no significant difference between diabetic and nondiabetic subjects among the pairs of groups, no heart failure patients (groups 1 and 2), heart failure patients (groups 3 and 4), and patients with a history of heart failure but presenting with dyspnea not due to heart failure (groups 5 and 6) (Fig. 1). Figure 2 illustrates the ROC curve analysis for the subset groups, also showing no significant difference in the AUC (0.87–0.88). When considering median BNP concentrations, the heart failure group with diabetes had slightly lower BNP concentrations than the heart failure group without diabetes ($P < 0.05$).

Table 2— *Analysis of subset groups (median age, sex, creatinine clearance, BMI matched, and NYHA heart failure classification)*

Group	*n*	Age (95% CI)	Percent women (95% CI)	Creatinine clearance (95% CI)	BMI (95% CI)	BNP (95% CI)
No diabetes and no heart failure	324	59 (57–62)	35.2 (30–40)	74.0 (68–77)	28.9 (28–30)	32.4 (27–39)
Diabetes and no heart failure	107	60 (56–65)*	33.0 (24–42)*	70.8 (63–79)*	30.4 (28–32)*	32.9 (24–50)*
No diabetes and heart failure†	247	70 (67–73)	43.3 (37–49)	52.7 (45–58)	28.8 (28–30)	587 (446–714)
Diabetes and heart failure‡	183	67 (64–70)*	42.6 (35–50)*	57.7 (45–52)*	30.2 (29–31)*	494 (377–661)*
No diabetes and heart failure history	41	70 (61–79)	53.7 (38–69)	48.4 (38–65)	25.7 (24–31)	180 (86–553)
Diabetes and heart failure history	20	73 (66–75)*	35.0 (14–56)*	63.2 (43–86)*	25.8 (24–32)*	120 (61–312)*

*P = NS; †mean (±SD) NYHA classification: 3.22 ±0.080; ‡mean (±SD) NYHA classification: 3.24 ± 0.083.

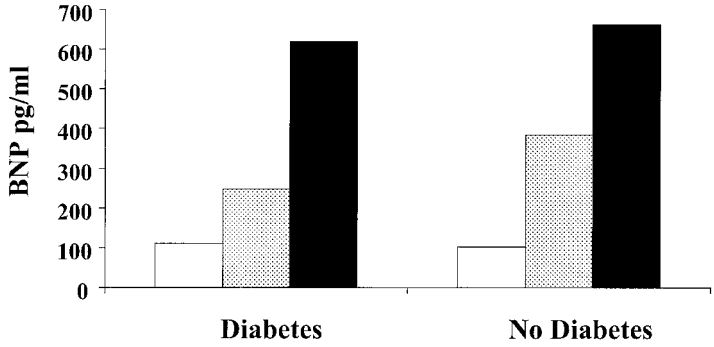

Figure 1—*BNP concentrations in patients with and without diabetes. □, no heart failure; ▨, history of heart failure but dyspnea due to other causes; ■, heart failure.*

Independent predictors of heart failure

A previous publication (11) from the Breathing Not Properly Multinational Study had tabulated the variables that were most useful as an independent predictor of heart failure using multiple logistic regression. Table 3 shows that the presence of diabetes is an independent factor for heart failure (odds ratio [OR] 1.61, 95% CI 1.1–2.3). The OR for the subgroup matched for age, sex, BMI, and estimated glomerular filtration rate was unchanged. The log BNP concentration was the most powerful predictor of heart failure (11.32, 8.24–15.02).

CONCLUSIONS — The identification of asymptomatic diabetic patients with left ventricular dysfunction can be potentially significant because therapeutic agents such as ACE inhibitors or angiotensin II receptor antagonists may be useful to reduce morbidity and mortality. In a subgroup consisting of diabetic patients in the Losartan Intervention For Endpoint (LIFE) trial, there was a significant reduction in composite cardiovascular morbidity and mortality (OR 0.87, 95% CI 0.77–0.98) for Losartan compared to atenolol in patients with hypertension and left ventricular hypertrophy (14). These findings have led some to question if tests should be implemented to screen asymptomatic subjects for heart failure (15). As such, there have been several studies that have examined the potential use of BNP as such a test. The North Glasgow MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) study produced an AUC of 0.88, of patients with left ventricular systolic dysfunction, when BNP was targeted at high-risk subjects aged >55 years with a history of prior ischemic heart disease (16). These AUCs were within the range of other widely used and accepted laboratory screening tests, such as prostate-specific antigen, Papanicolaou smear, and mammography (17). In contrast to the MONICA study, results from the Framingham Heart Study for BNP screening produced a different conclusion (18). The ROC AUC from blood tested for BNP on 3,177 subjects was ≤0.75, leading these investigators to suggest that mass screening for left ventricular dysfunction was not appropriate, even when high-risk subgroups were targeted (i.e., subjects who were aged ≥60 years, hypertensive, diabetic, and with known cardiovascular disease).

In this study, we attempted to determine whether diabetic patients symptomatic for heart disease produced higher BNP concentrations than nondiabetic patients, with and without confirmed heart failure. Our data showed that the mean BNP concentrations were identical in diabetic versus nondiabetic subjects who were matched in parameters known to affect BNP concentrations, i.e., age, sex, BMI, and renal function. Although diabetes was determined to be an independent predictor of heart failure (Table 3), the OR was very modest.

The data from the Breathing Not Properly Multinational Trial would suggest that diabetes status is not a confounding variable to be considered when interpreting BNP concentrations in patients who present acutely with dyspnea. Our results are in contrast to other studies where diabetic patients had higher BNP concentrations than nondiabetic ones. Given that symptomatic diabetic patients did not produce higher BNP results than matched nondiabetic subjects in our study, one might be tempted to suggest that screening asymptomatic diabetic patients would not be useful. However, Epshteyn et al. (9) screened diabetic patients with and without a clinical indication for echocardiography (CIE). Patients with CIE and subsequent abnormal left ventricular function (n = 112) had a mean BNP concentration of 435 ± 41 pg/ml compared with those with no CIE but who had abnormal left ventricular function on echo (161 ± 40 pg/ml, n = 32). Twenty-one of 32 patients with no CIE but with abnormal left ventricular function had diastolic dysfunction (BNP 190 ± 60 pg/ml). A ROC curve revealed that the AUC was 0.91 for patients with CIE and 0.81 for patients without CIE ($P < 0.001$). In those with no heart failure symptoms, BNP levels showed a high negative predictive value (91% for BNP values <39 pg/ml), whereas in patients who had a CIE, BNP levels showed a high positive predictive value for the detection of left ventricular dysfunction (96% with BNP levels >90 pg/ml).

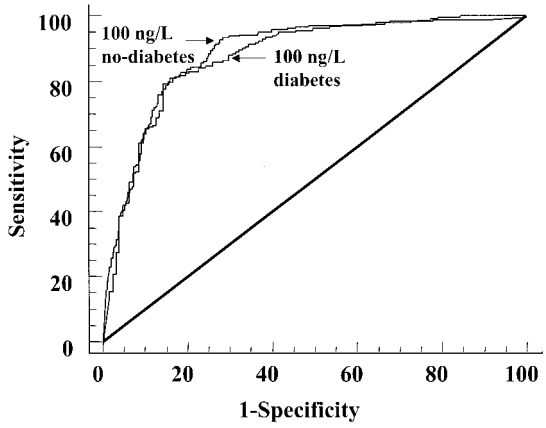

Figure 2—*ROC curve analysis for BNP in the age-, sex-, creatinine clearance–, and BMI-matched heart failure versus no heart failure patients. AUCs: no diabetes, 0.888 (95% CI 0.860–0.912); diabetes, 0.878 (0.837–0.913);* P = *NS.*

Table 3 —*Multivariate predictors of a final diagnosis of heart failure

Predictor	OR (95% CI)	*P*
Diabetes	1.61 (1.10–2.30)	0.01
History of heart failure	3.96 (2.80–5.61)	<0.0001
S3	3.70 (1.74–7.84)	0.0001
Positive NHANES score	1.94 (1.35–2.80)	<0.0001
Positive Framingham score	1.58 (1.09–2.03)	<0.0001
Clinical judgement (>80% certain of heart failure as final diagnosis)	6.91 (4.40–10.85)	<0.0001
Log BNP	11.31 (8.24–15.02)	<0.0001

NHANES, National Health and Nutrition Examination Survey.

In the present study, our excluded subjects included those with advanced renal dysfunction (estimated glomerular filtration rate $<15\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$). As renal failure is a major complication of diabetes, it may be possible that the patients tested in this study had milder forms of diabetes and did not have the initial stages of heart failure. In the study of Yano et al. (19), patients with diabetes and microalbuminuria had higher BNP concentrations than diabetic patients who had normal microalbuminuria. Nagai et al. (20) showed a difference in diabetic patients with nephropathy and/or retinopathy, but no difference in diabetic patients without albuminuria. Siebenhofer et al. (21) found that patients with mild or significant diabetic nephropathy had higher NH_2-terminal proBNP, the inactive circulating fragment of the BNP prohormone, than diabetic patients without albuminuria. In a commentary, Chan et al. (22) suggest a relationship between microangiopathy, as indicated by microalbuminuria or retinopathy, and BNP concentrations. Their notion was suggested following the report of Poirier et al. (23), who found a trend toward a higher incidence of microalbuminuric patients with abnormal left ventricular diastolic dysfunction (54%) than diabetic patients who had normal diastolic function, although their results had not reached statistical significance. Both BNP and atrial natriuretic peptide have been shown to increase tubular protein excretion of albumin and α1-microglobulin (24). This study would support the relationship of BNP and microalbuminuria. Unfortunately, in the Breathing Not Properly Multinational Study, fasting blood glucose, HbA_{1c}, and urine microalbumin levels were not measured in the database, thus no estimate of diabetes disease severity could be made.

Summary

In the Breathing Not Properly Trial, diabetic patients without heart failure had the same concentration of BNP than non–heart failure and nondiabetic patients who were matched by age, sex, BMI, and renal function. There was also no difference in BNP concentrations among patients with heart failure who were also matched for these parameters and for heart failure disease severity (NYHA classification). The presence of diabetes was an independent predictor of heart failure, but was not as powerful as the log of BNP concentration (OR 1.61 vs. 11.31, respectively). However, no conclusions can be rendered as to the role of BNP testing for screening asymptomatic diabetic patients for left ventricular dysfunction because the degree of disease severity among the diabetic patients could not be assessed.

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APPENDIX

The Breathing Not Properly Multinational Study Group

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