Utility of B-Type Natriuretic Peptide (BNP) as a Screen for Left Ventricular Dysfunction in Patients With Diabetes

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OBJECTIVE — Routine screening of diabetic patients with echocardiography is not feasible due to its limited availability and high cost. B-type natriuretic peptide (BNP) is secreted from the left ventricle in response to pressure overload and is elevated in both systolic and diastolic dysfunction.

RESEARCH DESIGN AND METHODS — BNP levels were compared to echocardiographic findings in 263 patients. Patients were divided into two groups: clinical indication for echocardiography (CIE) ($n = 172$) and those without clinical indication for echocardiography (no-CIE) ($n = 91$). Cardiologists making the assessment of left ventricular function were blinded when measuring plasma levels of BNP.

RESULTS — The 91 patients with no-CIE with echos had similar BNP levels (83 ± 16 pg/ml) to the 215 patients with no-CIE without echos (63 ± 10, $P = 0.10$). 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 had abnormal left ventricular function on echo ($n = 32$) (161 ± 40 pg/ml). Twenty-one of 32 patients with no-CIE but with abnormal left ventricular function had diastolic dysfunction (BNP 190 ± 60pg/ml). A receiver-operating characteristic (ROC) curve revealed that the area under the curve was 0.91 for CIE patients and 0.81 for no-CIE patients ($P < 0.001$). For those with no congestive heart failure (CHF) symptoms, BNP levels showed a high negative predictive value (91% for BNP values <39 pg/ml), while in those 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).

CONCLUSIONS — BNP can reliably screen diabetic patients for the presence or absence of left ventricular dysfunction.

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Diabetes has now reached epidemic proportions, affecting an estimated 110 million people worldwide. There are 16–17 million people with diabetes in the U.S., one-third of whom are undiagnosed (1,2). Diabetes is a major risk factor for increased cardiovascular morbidity and mortality rates (3). Current studies suggest that 11.8% of type 2 diabetic subjects have CHF (4). Cardiac involvement in diabetes covers a wide spectrum, ranging from asymptomatic silent ischemia to clinically evident heart failure (5). While echocardiography is considered the cornerstone of diagnostic evaluation in patients with suspected left ventricular dysfunction (6), its expense and limited accessibility in hospitals and especially clinics has led to increased interest in cost-effective strategies to detect abnormal ventricular function.

B-natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricle in response to left ventricular volume expansion and pressure overload. BNP levels are known to be elevated in patients with left ventricular dysfunction and correlate to New York Heart Association (NYHA) class and prognosis (7–11). In previous studies, especially those in which BNP was examined in relation to echocardiography, it was clear that patients with diabetes often had high BNP levels along with abnormal ventricular function (6,7,9–11). However, BNP has never been used prospectively to predict abnormal ventricular function in diabetic patients. We therefore sought to assess the association of BNP levels with ventricular dysfunction in outpatient diabetic patients, regardless of whether they had previously documented congestive heart failure (CHF).

RESEARCH DESIGN AND METHODS

Study population

This study was approved by the University of California, San Diego Institutional Review Board. The participants included 486 diabetic patients (88% type 2 diabetes, 12% type 1 diabetes) at the San Diego Veteran's Healthcare System studied between June 1999 and February 2001. Patients were recruited from the diabetes clinic ($n = 357$) and the echocardiography suite (while waiting for their scheduled appointment, $n = 129$). Two-hundred sixty-three patients who underwent echocardiography comprised the database. Patients were divided into two groups

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Abbreviations: AUC, area under the curve; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CIE, clinical indication for echocardiography; IVRT, isovolumetric relaxation time; no-CIE, no 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.

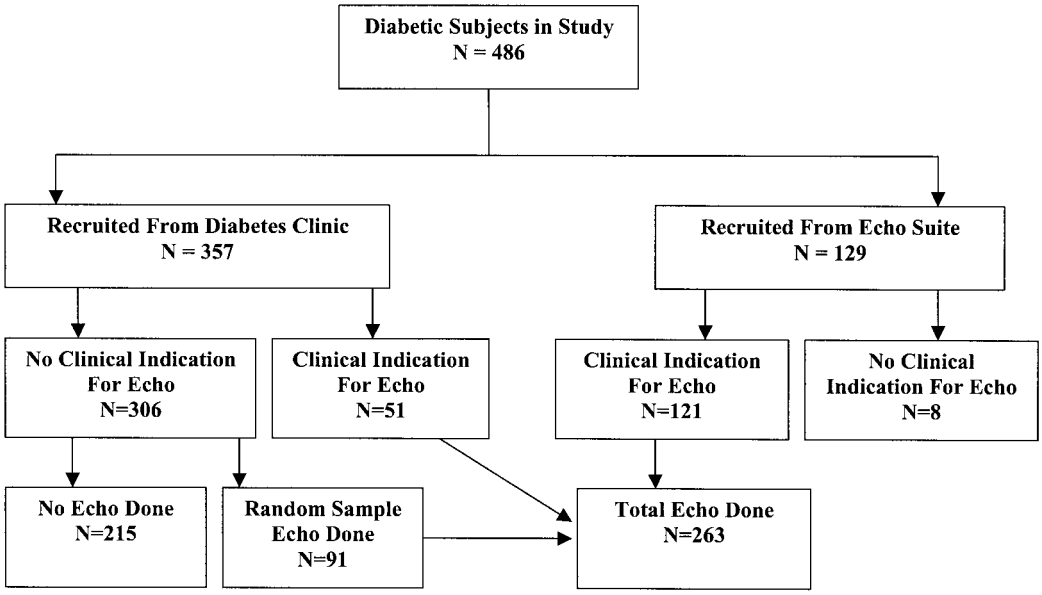

Figure 1—*Patient distribution and classification.*

depending on whether there was a clinical indication for echocardiography (CIE) (Fig. 1). Patients with a CIE met at least one of the following criteria: symptoms or signs of CHF (shortness of breath, lower extremity edema), history of CHF, or suspicion of left ventricular dysfunction by the physician. Of the 172 patients with CIE, 121 were recruited for the study at the time they were receiving their echo and 51 were in the diabetes clinic and had already either had an echo or were scheduled to receive one within 6 months of BNP draw. Eight patients from the echocardiography suite, whose referral was to assess valve disease, determine whether a vegetation was present, or rule out a cardiac cause of stroke, were excluded. Of the remaining 306 clinic patients with no CIE (no-CIE), a random sampling of ~33% (91 patients) received echocardiography within 6 months of BNP draw. Patient referrals were made either by clinic physicians or attending or nurse practitioners.

Echocardiography

Two-dimensional, M-mode, spectral, and color flow Doppler echocardiograms were obtained with commercially available instruments operating at 2.0–3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical four and two chamber views (12). Pulsed Doppler spectral recordings were obtained from a 4 × 4-mm sample volume placed at the tips of the mitral leaflets and in the pulmonary vein, adjusted to yield the maximal amplitude velocity signals. All data were hard copied to a 0.5-inch VHS videotape for subsequent playback, analysis, and measurement.

Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. Left ventricular systolic and diastolic volumes and ejection fractions were derived from biplane apical (two and four chamber) views using a modified Simpson's rule algorithm (13). The transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: E and A velocities as the peak values reached in the early diastole and following atrial contraction, respectively, and deceleration time as the interval from the E wave to the decline of the velocity to baseline. In addition, pulmonary venous systolic and diastolic flow velocities were obtained as the maximal values reached during the respective phase of the cardiac cycle, and the pulmonary venous "A" reversal as the maximal velocity of retrograde flow into the vein following the P wave of the ECG. Finally, the left ventricular isovolumetric relaxation time (IVRT) was obtained from the apical five-chamber view with a continuous wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the left ventricular outflow tract and mitral orifice so as to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmitral flow. IVRT was taken as the time in milliseconds from the end of ejection to the onset of left ventricular filling. Experienced cardiologists who were blinded to the BNP levels interpreted all echocardiograms.

Echo classifications

Normal ventricular function was defined as ejection fraction >50%, normal left ventricular end diastolic (3.5- 5.7 cm) and end systolic dimension (2.5–3.6 cm), and no major wall motion abnormalities.

Systolic dysfunction was defined as ejection fraction <50% or global hypokinesia or discrete wall motion abnormalities.

Diastolic dysfunction was defined as impaired relaxation and restrictive and pseudonormal pattern, based on the following definition: *1*) impaired relaxation: in patients <55 years of age E/A <1, deceleration time (DT) >240 ms. In patients >55 years of age E/A <0.8. Additional confirming evidence was isovolumic relaxation time (IVRT) >90 ms. *2*) Restrictive pattern: E/A >1.5 and DT <150 ms. Additional confirming evidence was pulmonary vein diastolic flow more than pulmonary vein systolic flow and pulmonary A-wave duration more than mitral A-wave duration. Pulmonary diastolic flow reversal, IVRT <70 ms. *3*) Pseudonormal: E/A >1, DT >240 ms. Confirmation by valsava when possible.

Systolic and diastolic dysfunction was defined as ejection fraction <50% with global hypokinesia or discrete wall mo-

tion abnormalities along with diastolic dysfunction as described above.

CIE

History of CHF was obtained from patients' medical records with one or more of the following objective findings: previous abnormal left ventricular function by echocardiography or nuclear scan, hospitalization for CHF, diagnosis of CHF made by cardiologist, or regular follow-up in the outpatient cardiomyopathy clinic. Patients with no history of CHF were additionally characterized by either lack of any prior study of left ventricular function or prior echocardiography with negative findings. The evidence of symptoms and suspicion of left ventricular dysfunction was obtained from the echocardiography consult form, where the provider requesting an echo detailed reasons for the echo request.

Measurement of BNP plasma levels

During initial evaluations, a small sample (5 ml) was collected into tubes containing potassium EDTA (1 mg/ml blood). BNP was measured using the Triage B- Type Natriuretic Peptide test (Biosite, San Diego, CA). The Triage BNP test is a fluorescence immunoassay for the quantitative determination of BNP in whole-blood and plasma specimens and has been recently characterized with regards to precision, analytical sensitivity, stability, and utility (14–16). BNP values were determined on site utilizing the point of care method with either whole-blood or plasma samples.

Statistics

Group comparisons of BNP values were made using *t* tests for independent samples and ANOVA with post hoc Tukey's tests where indicated. In all cases, these were computed with raw BNP values and repeated with log-transformed BNP values since the BNP distribution was positively skewed. Both versions yielded the same conclusions. Results are expressed as mean ± SE for raw values. Sensitivity, specificity, and accuracy were computed for BNP using a selection of possible cut points. The diagnostic utility of BNP alone was compared with the echocardiographic probability of left ventricular dysfunction using receiver-operating characteristic (ROC) curves. The results are expressed in terms of the area under the curve and the 95% CI for this area. Logistic regression was used in a multivariate approach for evaluating the ability of BNP to identify left ventricular dysfunction over and above the information provided by other indicators.

Table 1—*Characteristics of 263 patients referred for echocardiography*

Age (years) (means ± SE)	54 ± 1
Sex (men/women)	252/11
Normal left ventricular function	45%
Abnormal left ventricular function	55%
History of the following:	
CHF	25%
Hypertension	85%
Coronary artery disease	48%
Myocardial infarction	27%
Atrial fibrillation	15%
Type 1 diabetes	10%
Type 2 diabetes	90%
Renal failure	6%

RESULTS — The characteristics of all patients who underwent echocardiography are shown in Table 1. Fifty-five percent of patients had abnormal left ventricular function by echo. Nearly all patients had risk factors for heart disease, including 85% with hypertension and 48% with coronary artery disease.

The 91 patients with no-CIE who were randomly selected to receive echocardiography had similar BNP levels (83 ± 16 pg/ml) to the 215 patients with no-CIE who did not receive echocardiography (BNP 63 ± 10, $P = 0.10$). Table 2 shows that patients with CIE had higher rates of hypertension, coronary artery disease, myocardial infarction, and higher BNP levels (301 ± 31 pg/ml) than those with no-CIE ($P < 0.001$).

Figure 2 presents mean BNP values for those patients with normal and abnormal left ventricular function. In patients with normal left ventricular function, BNP levels were low, regardless of whether a CIE was present (51 ± 17 and 41 ± 7 pg/ml, respectively). Patients who had a CIE and were found to have subsequent abnormal left ventricular function ($n = 112$) had a mean BNP concentration of 435 ± 41 pg/ml. Patients who had no-CIE, yet who were found to have abnormal left ventricular function on echo ($n = 32$), had BNP levels of 161 ± 40 pg/ml. Differences between patients with abnormal and normal left ventricular function in both groups were significant ($P < 0.001$ in both cases).

With regards to treatment modalities, there were no differences in raw and log BNP levels to those taking or not taking ACE inhibitors or calcium channel blockers. However, patients taking diuretics, digitalis, and β-blockers had higher BNP levels than those not taking medication (diuretics vs. no diuretics: 171 ± 26 vs. 55 ± 8 pg/ml, $P < 0.001$; digitalis vs. no digitalis: 301 ± 73 vs. 70 ± 8 pg/ml, $P < 0.001$; β-blockers vs. no β-blockers: 158 ± 27 vs. 71 ± 9 pg/ml, $P = 0.001$).

Figure 3 presents BNP mean values for those patients with abnormal left ventricular function divided into purely systolic, purely diastolic, and the combination of systolic and diastolic. BNP levels for all abnormal left ventricular function groups are significantly higher than for all the normal left ventricular function groups. Of the 32 patients who had no-CIE, yet who had abnormal left ventricular function, the majority ($n = 21$) had diastolic dysfunction, with a mean BNP value of 190 ± 60, significantly different from those with normal left ventricular function (41 ± 7 pg/ml, $P < 0.001$).

The ability of BNP to differentiate patients with normal versus abnormal left ventricular function was assessed with an ROC curve analysis (Fig. 4). The area under the ROC curve, using BNP to separate normal versus abnormal left ventricular function in patients with a CIE, was 0.91 (95% CI 0.86–0.96, $P < 0.001$). A BNP cutoff value of 79 pg/ml had a sensitivity of 86%, a specificity of 92%, and an accu-

Table 2—*Patient characteristics: no-CIE versus CIE*

	no-CIE	CIE
Average BNP (pg/ml) (means ± SE)	83 ± 16	301 ± 31
History of		
Hypertension	81%	87%
Coronary artery disease	23%	62%
Myocardial infarction	18%	32%
Atrial fibrillation	4%	20%
Renal failure	3%	8%

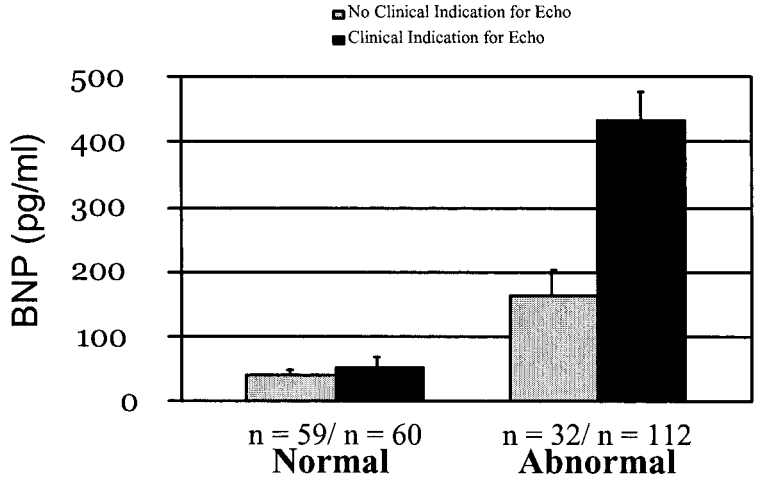

Figure 2—*Mean ± SE for normal and abnormal left ventricular dysfunction for patients with CIE and with no-CIE.*

racy of 88%. Levels of ≥79 pg/ml had a positive predictive value of 95% (Table 3).

The area under the ROC curve using BNP to separate normal versus abnormal left ventricular function in no-CIE patients was less than that for those with an indication, but still highly significant (AUC = 0.81, 95% CI 0.71–0.91, $P < 0.001$). In addition, a BNP cutoff value of 60 pg/ml had a sensitivity of 84%, a specificity of 76%, and an overall accuracy of 79%. Levels ≤60 pg/ml had a negative predictive value of 90% (Table 3).

Logistic regression was used in a multivariate approach for evaluating the ability of BNP to identify left ventricular dysfunction over and above the information provided by other indicators (Table 4). Historical variables and BNP were used as independent variables in this analysis and the presence of left ventricular dysfunction was the dependent variable. History of CHF, coronary artery bypass graft, and atrial fibrillation each contributed to the identification of left ventricular dysfunction, with BNP being the strongest predictor ($P < 0.001$).

CONCLUSIONS — The Framingham Study (17) firmly established the epidemiological link between diabetes and heart failure. The poor prognosis of heart failure in diabetic patients was demonstrated in a report from SOLVD (Studies of Left Ventricular Dysfunction) (18) where, compared with nondiabetic subjects, diabetic subjects were more likely to be admitted for heart failure and had mortality related to pump failure . In the presence of coronary disease, diabetes is an independent factor for progression of heart failure (19).

Early detection of left ventricular dysfunction enables administration of treatment that can improve survival and increased well-being (20,21). Treatment can delay progression from the precursor state, asymptomatic left ventricular dysfunction (22). However, ventricular dysfunction may be difficult to diagnose because patients may be asymptomatic or have nonspecific symptoms and abnormal findings on physical examination are often absent (23,24). Echocardiography, one of the fastest growing procedures in cardiology (25), is not feasible as a widespread screening test in the outpatient setting due to both its limited availability and expense.

BNP is a 32–amino acid polypeptide containing a 17–amino acid ring structure common to all natriuretic peptides (26). It is found mainly in the cardiac ventricles, and its release appears to be directly proportional to ventricular volume expansion and pressure overload (7,27,28). BNP is an independent predictor of high left ventricular end-diastolic pressure (7) and correlates to both NYHA and prognosis (29). A rapid assay for BNP has been approved for the diagnosis of CHF, and its use in this capacity has already been delineated in recently published heart failure guidelines (30).

To the limited extent that BNP has been used as a screening procedure in primary care settings, it has been shown to be a useful addition to the evaluation of possible CHF (31–33). In a study of 1,252 randomly selected subjects, a plasma BNP concentration ≥17.9 pg/ml had a sensitivity and specificity for left ventricular dysfunction of 77 and 87% for all participants and 92 and 72% for those ≥55 years of age, respectively (31). In a study of 122 consecutive patients with suspected new heart failure referred by general practitioners to a rapid-access heart failure clinic for diagnostic confirmation, a BNP level of 76 pg/ml, chosen for its negative predictive value of 98% for heart failure and similar to the cutoff in the

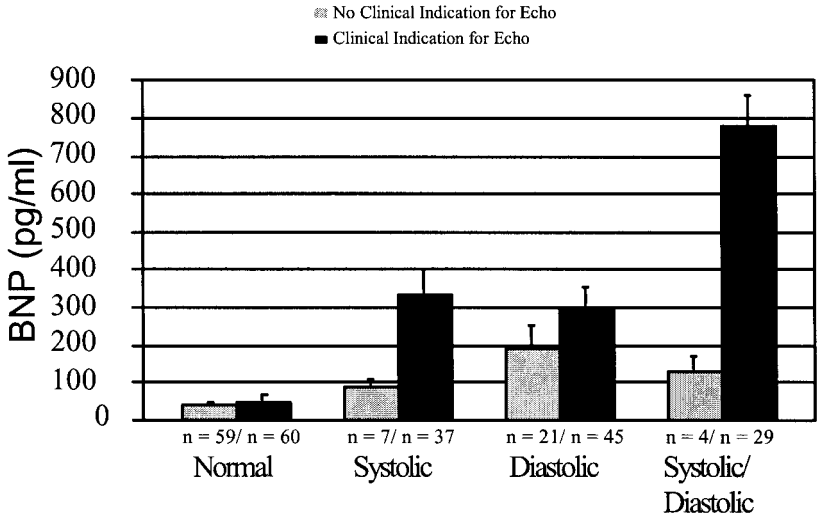

Figure 3—*BNP values for the different subclasses of left ventricular dysfunction, namely, all systolic, all diastolic, and all systolic plus diastolic dysfunction for patients with CIE and with no-CIE. Data are expressed as mean ± SE*

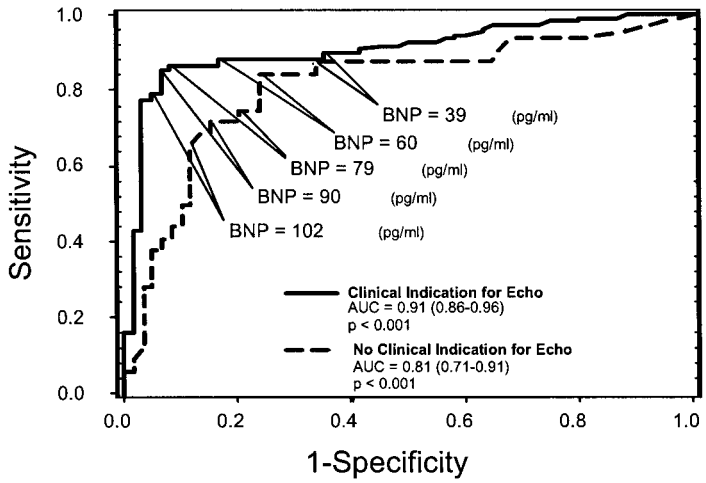

Figure 4—*ROC curves comparing the sensitivity and specificity of BNP and echocardiography diagnosis of left ventricular dysfunction for patients with CIE and with no-CIE.*

present study, had a sensitivity of 97%, a specificity of 84%, and a positive predictive value of 70% (33). Maisel et al. (9) characterized patients who had both echocardiography and BNP levels and found that of the patients with no documented history of CHF and no past determination of left ventricular function, 51% had abnormal echocardiographic findings. In this group, BNP levels were significantly higher (328 ± 29 pg/ml) than the 49% of patients with no history of CHF and a normal echocardiogram (30 ± 3, $P < 0.001$). In patients with a known history of CHF, with preciously documented left ventricular dysfunction, all had abnormal findings ($n = 102$) with elevated BNP levels (545 ± 45 pg/ml).

The ability of BNP to detect abnormal cardiac function (systolic or diastolic) has been assessed with ROC analysis (10). The area under the ROC curve using BNP to detect any abnormal echocardiographic finding was 0.952. A BNP value of 75 pg/ml had a sensitivity of 85%, a specificity of 97%, and an accuracy of 90% for predicting left ventricular dysfunction. In these as well as previous studies, it appeared that patients with diabetes often had high BNP levels, even when there was no previously documented history of heart failure (6,7,9–11). The current study specifically examined two groups of diabetic patients: those with high probability for left ventricular dysfunction (those with a CIE) and those with low probability for left ventricular dysfunction (no-CIE). Since BNP levels rise in proportion to the severity of cardiac dysfunction (34), it is not surprising that the group with CIE had higher BNP levels than those with no-CIE. The accuracy of BNP in detecting left ventricular dysfunction in diabetic patients (ROC curve analysis) is similar to that of the prostate-specific antigen for prostate cancer detection, Papanicolaou smears for cervical cancer, and mammography for the detection of breast cancer (35–37). In addition, for those with no symptoms of CHF, BNP levels showed a high negative predictive value in ruling out left ventricular dysfunction (91% for BNP values <39 pg/ml), while in those 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).

BNP levels in asymptomatic or minimally symptomatic diabetic patients

Despite the association between diabetes and increased cardiovascular morbidity and mortality rates, the prevalence of myocardial systolic and diastolic functional abnormalities in asymptomatic diabetic patients is not well defined. A recent echocardiographic study of 66 normotensive asymptomatic subjects with type 2 diabetes showed reduced left ventricular systolic and diastolic function compared with healthy subjects (38). Another study of 86 patients with type 2 diabetes free of cardiovascular disease found diastolic dysfunction in 41 of 86 patients (47%) (39). Diastolic dysfunction in type 2 diabetic patients is often found despite adequate metabolic control and freedom from clinically detectable disease (39). The National Institute of Health Sponsored Studies of left ventricular dysfunction in patients with asymp-

Table 3—*Sensitivity, specificity, positive and negative predictive values, and accuracy of various BNP levels in determining left ventricular function with use of echocardiography as the gold standard*

	BNP levels (pg/ml)	(%) Sensitivity	(%) Specificity	Positive predictive value (%)	Negative predictive value (%)	(%) Accuracy
CIE	39	90 (83–95)	65 (52–77)	83 (75–89)	78 (64–88)	81
	60	88 (81–93)	83 (71–91)	91 (84–95)	79 (67–88)	87
	79	86 (78–91)	92 (81–97)	95 (89–98)	77 (66–86)	88
	90	81 (73–88)	93 (84–98)	96 (89–99)	73 (61–82)	85
	102	79 (71–86)	95 (86–99)	97 (91–99)	71 (60–80)	85
no-CIE	39	88 (71–96)	66 (53–78)	58 (43–72)	91 (78–97)	74
	60	84 (66–95)	76 (63–86)	66 (49–80)	90 (78–96)	79
	79	75 (56–88)	76 (63–86)	63 (46–78)	84 (72–93)	76
	90	71 (53–86)	83 (71–91)	70 (51–84)	84 (72–92)	79
	102	66 (46–81)	88 (77–95)	75 (55–89)	82 (70–91)	80

Data are % (range) unless otherwise indicated. The different cut points were picked from the ROC curve.

Table 4—*Logistic regression was used in multivariate approach for evaluating the ability of BNP to identify left ventricular dysfunction over and above the information provided by other indicators*

	Coefficient B	SE	Degree of Freedom	*P*	Exponent of B*	95% CI for exponent of B*	
						Lower	Upper
History of CHF	1.64	0.57	1	0.004	5.20	1.70	15.80
Coronary artery disease	0.28	0.37	1	0.46	1.30	0.60	2.80
Coronary artery bypass grafting	0.69	0.54	1	0.20	2.00	0.70	5.70
Atrial fibrillation	1.68	0.87	1	0.04	5.30	1.10	25.90
Hypertension	0.90	0.52	1	0.08	2.40	0.90	6.80
$\log_{10}$ BNP	1.89	0.33	1	<0.001	6.60	3.50	12.60

All variables in this table and BNP were used as independent variables in this analysis and the presence of left ventricular dysfunction was the dependent variable. *Exponent of B as the odds ratio for noncontinuous variables (all except BNP).

tomatic left ventricular dysfunction demonstrated humoral activation characterized by increases in the natriuretic peptides without activation of the circulating renin-angiotensin system (18). In the present study, 21 of the 31 asymptomatic patients who had an abnormal echo had diastolic dysfunction, with BNP levels of 190 ± 60 pg/ml. While BNP levels cannot be used by itself to differentiate between systolic and diastolic dysfunction, a low BNP level in the setting of normal systolic function by echocardiography can likely rule out clinically significant diastolic dysfunction (11).

While the optimal treatment of diastolic heart failure has not been identified (40), occult coronary disease is a potentially reversible cause of diastolic dysfunction. It has been shown that myocardial ischemia augments the synthesis and release of BNP even in the absence of myocardial necrosis or preexisting left ventricular dysfunction. Reversible ischemia may transiently increase left ventricular wall stress, which may be sufficient to cause an elevation in BNP levels (41). Thus, elevated BNP levels may not only indicate left ventricular dysfunction but also be a marker for myocardial ischemia.

Limitations

This was an observational study done at a single Veteran's hospital, so one must be careful about generalizing the results to the entire population. Both the area under ROC curve and the negative predictive values are dependent on the patient population studied. Our population represents generally older, predominantly male veterans with a high prevalence of cardiac disease.

Echocardiographic recordings form the basis of the diagnosis of systolic and diastolic dysfunction in the current study. Numerous previous reports have validated the ability of cardiac ultrasonography to detect abnormalities of contractile function and to quantitate left ventricular volumes and ejection fraction (12,13). All patients in this study so designated had clear-cut evidence of left ventricular systolic dysfunction. Although diastolic dysfunction implies an abnormal relationship between left ventricular volume and pressure, echocardiography is capable of assessing only parameters related to volume. Therefore transmitral and pulmonary venous flow velocities provide only indirect measurements of diastolic performance. Nevertheless, these parameters have been shown to provide reliable markers of impaired diastolic function and are applied for this purpose in clinical practice.

Finally, in this study, BNP is being used to identify "any" impairment of ventricular function rather than "significant" impairment. Thus symptoms in such patients are not necessarily of cardiac origin and could challenge the value of labeling those patients as "abnormal" with BNP.

In summary, a rapid whole-blood test for BNP, which can be performed in the laboratory or the clinic, can reliably detect the presence or absence of left ventricular dysfunction in patients with diabetes, regardless of whether they have symptoms of left ventricular dysfunction. BNP levels should not replace imaging techniques in the diagnosis of CHF because these methods provide complementary information. However, a normal plasma concentration of BNP makes significant ventricular dysfunction unlikely. Elevated plasma concentrations warrant further cardiological evaluation. We believe that BNP may be a useful screening tool for left ventricular dysfunction, especially in the community of diabetic patients where the greatest risk of cardiac disease exists and where there is a limited access to echocardiography. In this setting, it is likely that BNP analysis would greatly assist in the appropriateness of patient referral and in optimization of drug therapy.

References

1. Eschwege E, Simon D, Balkau B: The growing burden of diabetes in the world population. *International Diabetes Federation Bulletin* 42:14–19, 1997
2. Centers for Disease Control and Prevention: *National Estimates and General Information on Diabetes in the United States: Diabetes Fact Sheet.* Atlanta, GA, US Dept of Health and Human Services, Centers of Disease Control and Prevention, 1997
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
4. Nichols GA, Hillier TA, Erbey JR, Brown JB: Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care* 24:1614–1619, 2001
5. Galderisi M, Anderson KM, Wilson PW, Levy D: Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiology* 68:85–89, 1991
6. Senni M, Rodeheffer RJ, Tribouilloy CM, Evans JM, Jacobsen SJ, Baily KR, Redfield MM: Use of echocardiography in the management of congestive heart failure in the community. *J Am Coll Cardiol* 33:124–170, 1999
7. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M : Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left

ventricular dysfunction. *Am Heart J* 135: 825–832, 1998
8. Harrison A, Morrison LK, Krishnaswamy P, Kazanegra R, Clopton P, Dao Q, Hlavin P, Maisel AS: B-type natriuretic peptide (BNP) predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann of Emerg Med* 39:131–138, 2002
9. Maisel AS, Koon J, Krishnaswamy P, Kazenegra R, Clopton P, Gardetto N, Morrisey R, Garcia A, Chiu A, De Maria A: Utility of B-natriuretic peptide (BNP) as a rapid, point-of-care test for screening patients undergoing echocardiography for left ventricular dysfunction. *Am Heart J* 141:367–374, 2001
10. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazenegra R, Wanner E, Gardetto N, Garcia A, de Maria A, Maisel AS: Utility of B-natriuretic peptide (BNP) in elucidating left ventricular dysfunction (systolic and diastolic) in patients with and without symptoms of congestive heart failure at a Veterans hospital. *Am J Med* 111:274–279, 2002
11. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS: Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 105:595–601, 2002
12. Feigenbaum H: *Echocardiography*. 6th ed. Philadelphia, Lea & Febiger, 1999
13. Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman NH, Brundage B, Botvinick EH, Boswell R, Carlsson E, Parmley WW : Left ventricular volume from paired biplane two-dimensional echocardiography. *Circulation* 60:547–555, 1979
14. Wieczorek SJ, Wu AH, Christenson R, Krishnaswamy P, Gottlieb S, Rosano T, Hager D, Gardetto N, Bailly KR, Maisel AS: A rapid B-Type natriuretic peptide (BNP) assay accurately diagnoses left ventricular dysfunction and heart failure: a multi-center evaluation. *Am Heart J* 144:834–839, 2002
15. Cheng VL, Krishnaswamy P, Kazanegra R, Garcia A, Gardetto N, Maisel AS: A rapid bedside test for b-type natriuretic peptide predicts treatment outcomes in patients admitted with decompensated heart failure. *JACC* 37:386–391, 2001
16. Kazanagra R, Chen V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, Maisel AS: A rapid test for B-type natriuretic peptide (BNP) correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Failure* 7:21–29, 2001
17. Kannel W, Hjortland M, Castelli W: Role of diabetes in congestive heart failure: the Framingham Study. *Am J Cardiol* 34:29–34, 1974
18. The SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325:293–302, 1991
19. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC, for the SOLVD Investigators: Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 77: 1017–1020, 1996
20. Pfeifer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial: the SAVE Investigators. *N Engl J Med* 327:669–677, 1992
21. Deveraux RB, Liebson PR, Horan MJ: Recommendations concerning use of echocardiography in hypertension and general population research. *Hypertension* 9:97–104, 1987
22. Nicklas JM, Pitt B, Timmis G, the SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 327:685–691, 1992
23. Stevenson LW: The limited availability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 261:884–888, 1989
24. Remes J, Miettinen H, Reunanen A, Pyorala K: Validity of clinical diagnosis of heart failure in primary health care. *Euro Heart J* 12:315–321, 1991
25. Krumholz HM, Douglas PS, Goldman L, Waksmonski C: Clinical utility of transthoracic two-dimensional and Doppler echocardiography. *J Am Coll Cardiol* 24: 125–131, 1994
26. Cheung BMY, Kumana CR: Natriuretic peptides: relevance in cardiac disease. *JAMA* 280:19839–19840, 1998
27. Nagagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, Nishino K, Yoshimasa T, Nakao K: Rapid transcriptional activation and early mRNA turnover of BNP in cardiocyte hypertrophy: evidence for BNP as "emergency" cardiac hormone against ventricular overload. *J Clin Invest* 96:1280–1287, 1995
28. Yoshimura M, Yasuce H, Okamura K, Ogawa H, Jougasaki M, Mukoyoma M, Nakao K, Imura H: Different secretion pattern of atrial natriuretic peptide and brain natriuretic peptide in patients with CHF. *Circulation* 87:464–469, 1993
29. Wallen T, Landahl S, Hedner T, Nako K, Saito Y: Brain natriuretic peptide predicts mortality in the elderly. *Heart* 77:264–267, 1997
30. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology: Guidelines for the diagnosis and treatment of chronic heart failure. *Euro Heart J* 22:1527–1560, 2001
31. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, Mc Murray JJV, Dargie HJ: Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351:9–13, 1998
32. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ: Symptomatic and asymptomatic left ventricular systolic dysfunction in an urban population. *Lancet* 350:829–833, 1997
33. Cowie MR, Struthers AD, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA, Sutton GC: Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 350:1347–51, 1997
34. Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H, et al: Brain natriuretic peptide as a novel cardiac hormone in humans. *J Clin Invest* 87:1402–1412, 1991
35. Jacobsen SJ, Bergstral EJ, Guess HA, Katusic SK, Klee GG, Osterling JE, Lieber ME: Predictive properties of serum prostate-specific antigen testing in a community-based setting. *Arch Int Med* 156:2462–2468, 1996
36. Swets JA, Getty DJ, Pickett RM, D'Orsi CJ, Seltzer SE, McNeil BJ: Enhancing and evaluating diagnostic accuracy. *Med Decision Making* 11:9–18, 1991
37. Fahey MT, Irwig L, Macaskill P: Meta-analysis of Pap test accuracy. *Am J Epid* 141:680–689, 1995
38. Annonu AK, Khaliq A, Fattah A, Mokhtar M, Ghareeb S, Elhendy A: Left ventricular systolic and diastolic abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. *J Am Soc Echocardiogr* 14:885–891, 2001
39. Zabalgoitia M, Ismaeil M, Anderson L, Maklady F: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. *Am J Cardiol* 87:320–323, 2001
40. Cody RJ: The treatment of diastolic heart failure. *Cardiology Clinics* 18:589–596, 2000
41. De Lemos J, Morrow D, Bentley J, Omland T, Sabatine M, McCabe C, Hall C, Cannon C, Braunwald E: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 345:10141021, 2001