



The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients

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Abstract *Aims:* We examined the usefulness of BNP for screening for left ventricular (LV) diastolic dysfunction in a sample of type 2 diabetic patients, without structural heart disorder, who have never presented symptoms or signs of heart failure (HF).

Methods and results: Seventy-six consecutive patients admitted to the Outpatient Diabetes Clinic were studied. Blood samples were analyzed using the Triage BNP fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). Echocardiography examinations were performed, with no knowledge of the BNP value. A total of 39 patients out of 76 (51%) were diagnosed with LV diastolic dysfunction and 23 (30%) with LV hypertrophy. Of the patients with LV diastolic dysfunction, impaired relaxation and pseudonormal pattern accounted for 97 and 3% of the cases, respectively. BNP levels among subjects with LV diastolic dysfunction (26 ± 22 pg/ml, $n = 39$) were not significantly different from patients with normal LV function (24 ± 23 pg/ml, $n = 37$ pg/ml; Mann–Whitney *U*-test, $Z = -0.4$, n.s.).

Conclusions: Our data confirm alarmingly high prevalence of LV diastolic dysfunction in asymptomatic individuals with diabetes. Identification of patients with preclinical diabetic cardiomyopathy should be a research and clinical priority. BNP levels cannot be used to detect mild LV diastolic dysfunction in this subset of patients, which requires Doppler echocardiography to be detected.

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Introduction

Patients with type 2 diabetes mellitus (DM) are affected by diabetic cardiomyopathy (DCM), a pre-clinical left ventricular (LV) diastolic dysfunction with preserved systolic function.^{1,4} DM is a well-recognized negative prognostic factor for morbidity and mortality for diabetic subjects with heart failure (HF).^{5–8} Hence there is a need, in diabetic patients, for identifying those with asymptomatic left ventricular diastolic dysfunction, at risk of developing clinical HF. LV diastolic dysfunction requires echocardiography to be diagnosed, but this test is not available for routine diagnostic screening,⁹ therefore alternative diagnostic procedures will be helpful. It has been recently demonstrated¹⁰ that B-type natriuretic peptide (BNP) may be a useful screening tool for LV diastolic and/or systolic dysfunction in the community of diabetic patients, confirming previous pilot reports.^{11–14}

Aims

The aim of our study was to examine the usefulness of BNP for screening for LV diastolic dysfunction in a sample of type 2 diabetic patients, without structural heart disorder, who have never presented symptoms or signs of HF.

Materials and methods

Study population

We screened 79 consecutive patients admitted to the Outpatient Diabetes Clinic. In order to be eligible for the study, patients had to simultaneously meet the following inclusion criteria:

- high risk of cardiovascular events¹⁵;
- no symptoms suggestive of HF¹⁶;
- no previous diagnosis of heart failure or structural heart disorders, including ischaemic heart disease;
- normal LV systolic function, defined as an LV ejection fraction (LVEF) > 50%, a normal LV end diastolic diameter, no major wall abnormalities, except for LV hypertrophy, on echocardiographic examination.

Three patients were excluded because they met ≥ 1 exclusion criterion on echocardiographic examination.

BNP assay

Blood samples were obtained from patients after 30 min of bed rest. Samples were immediately analyzed using the Triage BNP fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA).

Doppler echocardiography

Echocardiography tests were carried out using a Vingmed System Five device. The LVEF was measured using Simpson's biplane method. Diastolic indexes were acquired over 10 consecutive beats using sweep speeds of 50 and 100 cm/s. With pulsed-wave Doppler, we acquired transmitral flow using a 1–2 mm sample volume placed at the mitral leaflet tips in the apical four-chamber view and pulmonary venous flow using a 4-mm sample volume placed in the right upper pulmonary vein (PV). All images were measured by experienced investigators, who were blind to the clinical and BNP data. Measurements were averaged over three cycles and from pulsed-wave Doppler included transmitral peak *E* and *A* velocities and early deceleration time (DT) and PV systolic (*S*), diastolic (*D*), and atrial reversal (AR) flows.¹⁷ The classification of diastolic function was a predefined modification of classifications used in prior studies^{13,17,18}: (1) impaired relaxation with a normal pattern ($E/A < 1$ and deceleration time (DT) > 220 ms in subjects aged < 55 years or $E/A < 0.8$ and deceleration time > 220 ms in subjects aged > 55 years, PV *S/D* ratio > 1, and AR < 35 cm/s); (2) pseudonormal (E/A 1–2, DT 150–220 ms, PV *S/D* ratio < 1, and AR > 35 cm/s); (3) restrictive ($E/A > 2$, DT ≤ 150 ms, *S/D* ratio < 1, and AR > 35 cm/s). In patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: (1) restrictive pattern (DT ≤ 150 ms) or (2) indeterminate (DT > 150 ms). LV hypertrophy was defined as LV mass indexed to a body surface area of > 131 g m⁻² in men and 100 g m⁻² in women.¹⁹

Statistics

The data are expressed as mean \pm standard deviation. A *P*-value < 0.05 was considered significant. Categorical data are presented as numbers (percent), and continuous data as means + standard deviation. We used the Mann–Whitney *U*-test for the comparisons between samples, while the association between variables was verified with Fisher's exact test. Univariate logistic regression analysis was used to examine the relation of BNP

levels with the presence of LV diastolic dysfunction. An ROC (receiver-operated curve) was traced to test whether BNP values could be used to identify patients with LV diastolic dysfunction. Analyses were performed using SPSS software for Windows, release 12.0 (SPSS Inc., Chicago, USA).

Results

The characteristics of the study patients are shown in Table 1. The median age was 61 ± 7 years; 75% were men. They suffered by numerous comorbidities, particularly carotid atherosclerosis (28%), peripheral vessel atherosclerosis (20%), claudicatio intermittens (10%), and previous stroke/TIA (5%) (Table 1). All patients had type 2 diabetes.

A total of 39 patients out of 76 (51%) were diagnosed with LV diastolic dysfunction and

23 (30%) with LV hypertrophy (Table 1). Of the patients with LV diastolic dysfunction, impaired relaxation accounted for 97% of the cases, and pseudonormal pattern for 3% (Table 1). Table 1 illustrates the demographic characteristics (clinical, laboratory and instrumental) of subjects identified as suffering from LV dysfunction, and the rest of the study sample. There was a statistical difference between patients with LV diastolic dysfunction and those without, in terms of more frequent presence of hypertension, left atrial dilatation, ACE-inhibitors and thiazide diuretics prescription (Table 1).

Among the study population, the mean BNP value was 25 ± 22 pg/ml. BNP levels were correlated significantly with serum creatinine (Spearman-Rho = 0.28, n.s.), while no significant correlations were found between BNP and age or body mass index (Spearman-Rho = 0.18, and 0.15,

Table 1 Demographic, clinical, and instrumental characteristics of 76 asymptomatic diabetic patients

Parameter	Left ventricular diastolic dysfunction (<i>n</i> = 39)	No left ventricular diastolic dysfunction (<i>n</i> = 37)	All (<i>n</i> = 76)
Age (years)	61 ± 7	62 ± 8	61 ± 7
Male gender (%)	67	84	75
<i>Echocardiographic parameters (%)</i>			
Left ventricular ejection fraction (%)	69 ± 8	66 ± 8	67 ± 8
LV diastolic dysfunction	100	0	51
Impaired relaxation pattern	97.4**	0	50
Pseudonormal pattern	2.6**	0	1
Restrictive pattern	0	0	0
Left ventricular hypertrophy	36	24	30
Left atrium dilatation (> 40 mm)	60*	21	41
B-type natriuretic peptide (pg/ml)	26 ± 22	24 ± 23	25 ± 22
Body mass index	29 ± 3	29 ± 5	29 ± 4
Blood glucose (mg/dl)	184 ± 64	200 ± 63	191 ± 64
Total cholesterol (mg/dl)	213 ± 40	201 ± 28	208 ± 35
Triglycerides (mg/dl)	141 ± 95	110 ± 53	126 ± 78
Serum creatinine (mg/dl)	1.1 ± 0.3	1.0 ± 0.3	1.0 ± 0.3
HbA1c (g/dl)	7.6 ± 2.2	8.0 ± 2.0	7.8 ± 2.1
<i>Co-morbidities (%)</i>			
Hypertension	77**	49	63
Valve disease	0	0	0
Kidney failure (creatinine >2.5 mg/dl)	0	0	0
Carotid atherosclerosis	26	30	28
Peripheral vessel atherosclerosis	15	24	20
Previous stroke/TIA	8	3	5
<i>Current treatment (%)</i>			
ACE-inhibitors	67*	38	53
Angiotensin receptor blockers	18	19	18
Beta-blockers	3	8	5
Thiazide diuretics	33*	11	22
Insulin	54	35	45

Data are expressed as mean \pm SD, unless otherwise specified. **P* < 0.05 and ***P* < 0.01 vs "no left ventricular diastolic dysfunction"; Fisher's exact test.

respectively; n.s.), probably due to the small sample size. BNP levels among subjects with LV diastolic dysfunction (26 ± 22 pg/ml, $n = 39$) were not significantly different from patients with normal LV function (24 ± 23 pg/ml, $n = 37$ pg/ml; Mann–Whitney U -test, $Z = -0.4$, n.s.). Fig. 1 shows the receiver-operator characteristic curve for BNP in the diagnosis of LV diastolic dysfunction in the study population. The area under the curve was 0.53, and the confidence interval 0.39–0.66. BNP levels did not differ in relation to the presence of LV hypertrophy, being 27 ± 26 in patients with the latter vs 24 ± 21 pg/ml in the remaining diabetics (Mann–Whitney U -test, $Z = -0.7$, n.s.). Restriction of the analysis to patients with evidence of LV diastolic dysfunction and/or LV hypertrophy did not significantly increase sensitivity and specificity (AUC 0.54; CI: 0.40–0.67). Univariate regression did not find BNP levels as predictors of LV diastolic dysfunction.

Discussion

Our study confirms that asymptomatic patients with type 2 DM, free of structural heart disorders, have high prevalence rates of subclinical LV diastolic dysfunction, with preserved systolic function.^{1–4} Mild LV diastolic dysfunction may be the first stage of diabetic cardiomyopathy.^{20,21} It has been recently reported that diabetes results in functional, biochemical, and morphologic myocar-

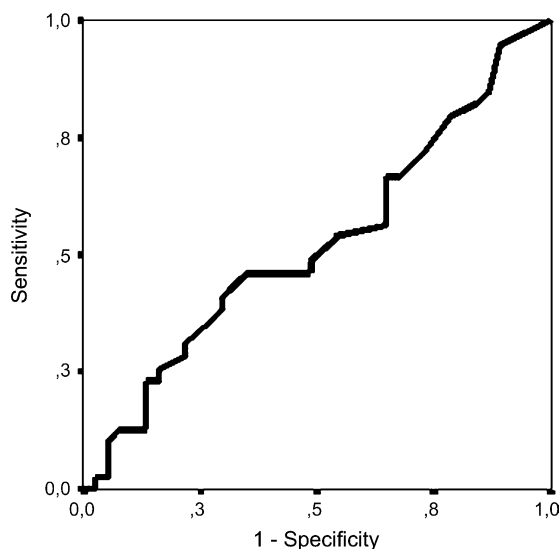


Figure 1 ROC (receiver operating curve) in 76 asymptomatic diabetic patients to compare the sensitivity/specificity of the BNP values with the presence of left ventricular diastolic dysfunction. The AUC (area under the curve) is 0.53 and the confidence interval 0.39–0.66.

dial abnormalities independent of hypertension and coronary heart disease, leading to impaired diastolic function and to clinical diastolic heart failure (DHF) (see²² for a review).

DHF is a disorder with a growing epidemiological impact, characterised by frequent episodes of instability, with high rates of mortality and admission to hospital (see²³ for a review). Around 30% of patients with DHF have diabetes.²² Although it is still not clear whether any drug intervention changes the prognosis of DHF patients, other than hypertension control,²⁴ diastolic function may be improved by aerobic exercise²⁵ and angiotensin converting enzyme inhibitors²⁶ and tight glycemic control decreases the risk of HF in individuals with diabetes.²⁷ Hence there is a need, in diabetic patients, for identifying those with initial diastolic impairment.

Unfortunately, our data do not support a possible role of natriuretic peptides as a procedure for screening mild LV diastolic dysfunction in asymptomatic diabetic patients. Previous studies showed that patients with DM had high BNP levels along with left ventricular dysfunction.^{10–14} However, these studies included patients with both systolic and (even severe) diastolic dysfunction. In our sample of asymptomatic diabetic patients, impaired relaxation cannot be identified using BNP levels, probably due to no or slight elevation of the LV filling pressures. This is consistent with previous reports by Dahlstrom²⁸ (in a sample of patients with isolated diastolic dysfunction and relaxation abnormalities), and Zhi²⁹ (in a large sample of subjects with subclinical diastolic and/or systolic LV dysfunction).

This study has many limitations. It is a single center study, which enrolled a small sample. Furthermore, the parameters of diastolic function assessed are all highly load dependent and do not entirely reflect LV diastolic dysfunction.

In conclusion, our data confirm alarmingly high prevalence of LV diastolic dysfunction in asymptomatic individuals with diabetes. Identification of patients with preclinical DCM should be a research and clinical priority. BNP levels cannot be used to detect mild LV diastolic dysfunction in this subset of patients, which requires Doppler echocardiography to be detected.

References

1. Di Bonito P, Cuomo S, Moio N, Sibilio G, Sabatini D, Quattrin S, et al. Diastolic dysfunction in patients with NIDDM of short duration. *Diabet Med* 1996;13:321–4.
2. Sanchez-Barriga JJ, Rangel A, Castaneda R, Flores D, Frati AC, Ramos MA, et al. LV diastolic dysfunction

- secondary to hyperglycemia in patients with type 2 diabetes. *Arch Med Res* 2001;**32**:44–7.
3. Beljic T, Miric M. Improved metabolic control does not reverse LV filling abnormalities in newly diagnosed NIDDM patients. *Acta Diabetol* 1994;**31**:147–50.
 4. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, et al. Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. *J Am Coll Cardiol* 2003;**42**:328–35.
 5. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;**34**:29–34.
 6. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;**35**:1628–37.
 7. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM, et al. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med* 1999;**106**:605–12.
 8. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 2003;**26**:2433–41.
 9. Francis CM, Caruana L, Kearney P, Love M, Sutherland GR, Starkey IR, et al. Open access echocardiography in management of heart failure in the community. *Br Med J* 1995;**310**:634–6.
 10. Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudalier S, et al. Utility of B-Type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. *Diabetes Care* 2003;**26**:2081–7.
 11. 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* 1998;**135**:825–32.
 12. Maisel AS, Koon J, Krishnaswamy P, Kazanegra R, Clopton P, Gardetto N, et al. 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* 2001;**141**:367–74.
 13. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E, et al. 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* 2002;**111**:274–9.
 14. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 2002;**105**:595–601.
 15. <http://www.siditalia.it> – Linee Guida per la prevenzione cardiovascolare del paziente diabetico.
 16. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of CHF. The Framingham study. *N Engl J Med* 1971;**285**:1442–6.
 17. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998;**32**:865–75.
 18. Troughton RW, Prior DL, Pereira JJ. Plasma B-type natriuretic peptide levels in systolic heart failure importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol* 2004;**43**:416–22.
 19. Kuch B, Hense HW, Gneiting B, Doring A, Muscholl M, Brockel U, et al. Body composition and prevalence of left ventricular hypertrophy. *Circulation* 2000;**102**:405–10.
 20. Seneviratne BI. Diabetic cardiomyopathy: the preclinical phase. *Br Med J* 1977;**1**:1444–6.
 21. Raev DC. Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. *Diabetes Care* 1994;**17**:633–9.
 22. Piccini J, Klein L, Gheorghide M, Bonow RO. New insights into diastolic heart failure: role of diabetes mellitus. *Am J Med* 2004;**116**(5A):645–755.
 23. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? *J Am Coll Cardiol* 2001;**38**:1277–82.
 24. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–81.
 25. Forman DE, Manning WJ, Hauser R, Gervino EV, Evans WJ, Wei JY, et al. Enhanced LV diastolic filling associated with long-term endurance training. *J Gerontol* 1992;**47**:M56–8.
 26. Hoffmann U, Globits S, Stefenelli T, Loewe C, Kostner K, Frank H, et al. The effects of ACE inhibitor therapy on LV myocardial mass and diastolic filling in previously untreated hypertensive patients: a cine MRI study. *J Magn Reson Imaging* 2001;**14**:16–22.
 27. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;**103**:2668–73.
 28. Dahlstrom U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? *Eur J Heart Fail* 2004;**2004**(6):281–7.
 29. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH. Screening for heart disease in diabetic subjects. *Am Heart J* 2005;**149**:349–54.