Heart Vessels (2008) 23:181–186
DOI 10.1007/s00380-007-1022-9

ORIGINAL ARTICLE

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Clinical value of B-type natriuretic peptide for the assessment of left ventricular filling pressures in patients with systolic heart failure and inconclusive tissue Doppler indexes

Received: May 28, 2007 / Accepted: September 21, 2007

Abstract Invasive hemodynamic monitoring with Swan-Ganz catheterization to guide treatment decisions in heart failure may be hazardous and may lack prognostic value. We assessed the clinical utility of B-type natriuretic peptide (BNP) in estimating left ventricular filling pressures in patients with inconclusive tissue Doppler indexes. In this study, 50 patients with systolic heart failure and an early transmitral velocity to early diastolic mitral annular velocity ratio (E/Ea) between 8 and 15 were studied. Among them, 25 had been admitted for acutely decompensated heart failure (group A) and the remainder were clinically stable outpatients (group B). All patients underwent simultaneous invasive pulmonary capillary wedge pressure (PCWP) determination, BNP measurement, and echocardiogrpaphy. In group A, BNP correlated with PCWP ($r = 0.803$, $P < 0.001$), deceleration time (DT, $r = –0.602$, $p = 0.001$), and end-systolic wall stress (SWS, $r = 0.565$, $P = 0.003$). In multivariate analysis, BNP was the only parameter independently associated with PCWP ($P = 0.023$). In group B, no correlation was found between BNP and PCWP or SWS, while DT correlated significantly with both PCWP ($r = –0.817$, $P < 0.001$) and BNP ($r = –0.8$, $P < 0.001$). We conclude that BNP may be a useful noninvasive tool for the assessment of left ventricular filling pressures in patients with acutely decompensated heart failure and inconclusive tissue Doppler indexes.

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Key words B-type natriuretic peptide · Left ventricular filling pressure · Heart failure · Doppler echocardiography · Tissue Doppler imaging

Introduction

Quantification of pulmonary capillary wedge pressure (PCWP) with the Swan-Ganz pulmonary artery catheter has long been used to optimize treatment in patients with heart failure. However, this monitoring technique is invasive, expensive, and occasionally hazardous to the patient. Moreover, there is recent evidence that it has a neutral effect, if not adverse, in terms of clinical outcome.[1–4]

Recent investigations have shown that the ratio of pulsed Doppler transmitral flow velocity in early diastole (E) to the early diastolic mitral annular velocity (Ea) measured by tissue Doppler echocardiography (TDI) is a simple noninvasive measurement that can predict left ventricular filling pressures (LVFP).[5,6] However, although a ratio above 15 correlates with elevated LVFP, values between 8 and 15 constitute a "gray zone" with a considerable variability of the underlying LVFP.[6]

B-type natriuretic peptide (BNP) is a 32-amino acid peptide hormone secreted by the myocardium in response to stretch and its plasma levels have been shown to correlate positively with LVFP measured invasively in patients with depressed ejection fraction and chronic heart failure.[7–11] The aim of the present study was to assess whether BNP correlates with LVFP in patients with systolic heart failure and an inconclusive E/Ea ratio, using invasively measured PCWP as the reference standard.

Subjects and methods

Patient population

Our study population consisted of 50 patients (39 men, aged 68.7 ± 8.5 years) with a left ventricular ejection fraction

<35% and an E/Ea ratio between 8 and 15. Among them, 25 consecutive patients (19 men, aged 68.5 ± 8.2 years) had been admitted to the hospital for acutely decompensated heart failure (group A), and another 25 consecutive ones (20 men, aged 68.9 ± 8.9 years) were clinically stable outpatients in New York Heart Association (NYHA) class II, under optimal medical therapy according to AHA/ACC guidelines, followed regularly in the heart failure clinic of our department (group B). Among group A patients, 20 had a known history of chronic heart failure, whereas in the remainder the diagnosis of acute heart failure was established upon admission.

Eligible patients were 18–85 years of age while exclusion criteria were atrial fibrillation, paced rhythm, mitral stenosis, severe mitral regurgitation, severe mitral annular calcification, mitral valve surgery, severe aortic stenosis (maximal aortic velocity >4 m/s), severe aortic regurgitation, pericardial effusion, acute coronary syndromes within 72 h, and impaired renal function (estimated glomerular filtration rate <60 ml/min). The study was approved by the institutional ethics committee, and written consent was obtained from each patient.

Echocardiography

Comprehensive transthoracic echocardiography was performed by an experienced operator who was blinded to patients' clinical data, BNP concentration, and invasive hemodynamic measurements, using a commercially available SSA-380A Toshiba Powervision machine. Two-dimensional and color Doppler imaging were performed in standard parasternal and apical views. Two-dimensional measurements were performed according to the recommendations of the American Society of Echocardiography and included ejection fraction by the previously described multidiameter method.[12,13]

Transmitral flow velocity signals were obtained in the four-chamber view by placing a pulsed Doppler sample volume at the tips of the valve leaflets; the peak velocity of early (E) and late (A) filling, and the deceleration time (DT) of the E-wave velocity were measured. End-systolic meridional wall stress (SWS) was calculated using the formula: systolic blood pressure × 1.35/4 × posterior wall thickness × [(1 + posterior wall thickness)/left ventricular end-systolic dimension].[14]

Tissue Doppler imaging (TDI) was acquired with standard presets optimized to eliminate background noise and enhance tissue signals using a 5–10-mm sample volume placed at the lateral and septal mitral annular margins in the apical four-chamber view. Tissue Doppler imaging measurements were performed in the catheterization laboratory immediately after PCWP measurement. The parameters measured were the peak systolic velocity (Sa), and the early (Ea) and late (Aa) diastolic velocities. The E/Ea ratio was computed from the average of the septal and lateral Ea, because this approach has been shown to yield optimum accuracy in patients with regional wall motion abnormalities.[15] All the above-mentioned Doppler velocities were obtained during normal expiration and five cardiac cycles were averaged.

Brain natriuretic peptide determination

Venous blood for BNP measurement was drawn at the time of invasive measurement and was immediately analyzed using Triage System for BNP (Biosite diagnostics, La Jolla, CA, USA), a test based on fluorescence immunoassay. This test has a range of 5–5000 pg/ml, with an average 95% analytical sensitivity of 0.2–4.8 pg/ml. Coefficients of variation are 10.1%, 12.4%, and 16.2% for mean values 28.8, 584.4, and 1 080.4 pg/ml. The median value of three consecutive readings of the same test device was used for the final analysis.

Right heart catheterization and measurements

Right heart catheterization was performed within 24 h upon admission using a 7-F, flow-directed Swan-Ganz catheter, which was introduced via the femoral vein. The catheter was advanced under fluoroscopic control to the wedge position to measure the PCWP. Then it was withdrawn sequentially through the pulmonary artery, the right ventricle, and the right atrium. Mean right atrial pressure (RAP), right ventricular pressure (RVP), systolic, diastolic, mean pulmonary artery pressure (PAP), and PCWP measurements were averaged from 5 consecutive beats in each position.

Statistical analysis

Statistical analysis was performed using the SPSS 10.0 statistical software package (SPSS, Chicago, IL, USA). Categorical variables were compared using the chi-square test. Mean values of continuous variables were compared between groups using Mann–Whitney *U*-test or Student's *t*-test, according to whether variables were normally distributed or not, as tested by the Kolmogorov–Smirnov test. Bivariate correlation (Pearson's correlation coefficient) was used to investigate for potential relationships between variables. Multiple linear regression analysis was used to identify independent correlates of PCWP. Receiver operator characteristics (ROC) analysis was performed to evaluate the ability of BNP to predict an increased PCWP, defined as >22 mmHg. Continuous variables are expressed as mean ± SD. A P value of less than 0.05 was considered statistically significant.

Results

The clinical characteristics of the patients enrolled are listed in Table 1. No difference was found regarding demographic and clinical data between the two groups. Echocardiographic and hemodynamic measurements and BNP levels are shown in Table 2.

Table 1. Clinical characteristics of the study population

	Group A ($n = 25$)	Group B ($n = 25$)	P value
Age, years	68.9 ± 8.9	68.5 ± 8.2	NS
Male sex	20 (80)	19 (76)	NS
Current smoking	5 (20)	8 (32)	NS
Treated hypertension	13 (52)	14 (56)	NS
Diabetes	5 (20)	5 (20)	NS
Hypercholesterolemia	9 (36)	8 (32)	NS
Heart failure etiology			
Ischemic	20 (80)	21 (84)	NS
Dilated	5 (20)	4 (16)	NS
Medications			
Loop diuretics	15 (60)	21 (84)	NS
Spironolactone	6 (24)	15 (60)	0.021
ACE inhibitors	17 (68)	24 (96)	0.023
ARBs	1 (4)	1 (4)	NS
Digoxin	5 (20)	7 (28)	NS
Beta-blockers	5 (20)	23 (92)	<0.001

Data are in absolute number (percentage data)
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NS, not significant

Table 2. Echocardiographic parameters, hemodynamic measurements, and BNP levels in the two study groups

	Group A ($n = 25$)	Group B ($n = 25$)	P value
LV end-diastolic diameter, mm	67 ± 5	67 ± 4	NS
LV ejection fraction %	25 ± 5	26 ± 7	NS
SWS, kdyne/cm^2	476 ± 97	419 ± 92	<0.05
Heart rate, beats/min	82.7 ± 10.1	60.6 ± 5.4	<0.001
Blood pressure, mmHg	120.6 ± 16.1	109.2 ± 9.6	<0.05
E/A	2.45 ± 1.19	2.34 ± 1.15	NS
DT, ms	118 ± 9	171 ± 20	<0.001
E/Ea	10.80 ± 2.10	10.00 ± 1.50	NS
RAP, mmHg	5.7 ± 1.85	4 ± 1.6	<0.005
PCWP, mmHg	23 ± 3	15 ± 3	<0.001
BNP, pg/ml	879 ± 145	130 ± 126	<0.001

Values are expressed as mean values ± standard deviation
LV, left ventricular; SWS, end-systolic meridional wall stress; E, peak early transmitral diastolic velocity; A, peak late transmitral diastolic velocity; DT, E deceleration time; Ea, peak early diastolic mitral annular velocity; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; BNP, B-type natriuretic peptide; NS, not significant

The reason for decompensation in group A patients was fluid overload in 9 patients, infection in 5, noncompliance to the prescribed regimen in 4, recently coprescribed drugs (such as nonsteroidal anti-inflammatory drugs) in 2, uncontrolled hypertension, thyroid dysfunction, and alcohol abuse in 1 patient each factor. The triggering cause was not clear in the remaining 2 patients.

In group A, univariate analysis revealed a positive correlation between BNP and both PCWP and SWS ($r = 0.803$, $P < 0.001$, Fig. 1, and $r = 0.565$, $P = 0.003$, respectively) and a negative correlation between BNP and DT ($r = –0.602$, $P = 0.001$). In a multivariate analysis concerning BNP, DT, and SWS as independent variables and PCWP as the dependent one, only BNP was still correlated with PCWP ($P = 0.023$). In group B, no correlation was found between BNP and either PCWP or SWS ($r = 0.060$, $P = 0.976$ and $r = 0.100$, $P = 0.636$, respectively), while a negative correlation was found between DT and PCWP ($r = –0.817$, $P < 0.001$, Fig. 2) and DT and BNP ($r = –0.8$, $P < 0.001$).

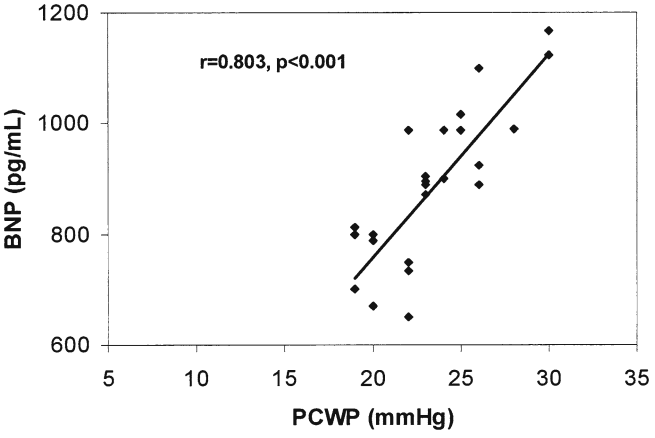

Fig. 1. Correlation between B-type natriuretic peptide (*BNP*) and pulmonary capillary wedge pressure (*PCWP*) in group A (patients with acutely decompensated heart failure)

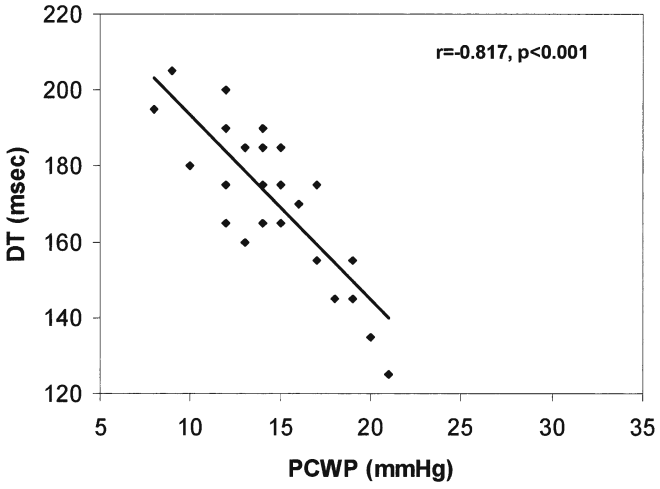

Fig. 2. Correlation between transmitral E-wave deceleration time (*DT*) and pulmonary capillary wedge pressure (*PCWP*) in group B (stable heart failure patients under optimal treatment)

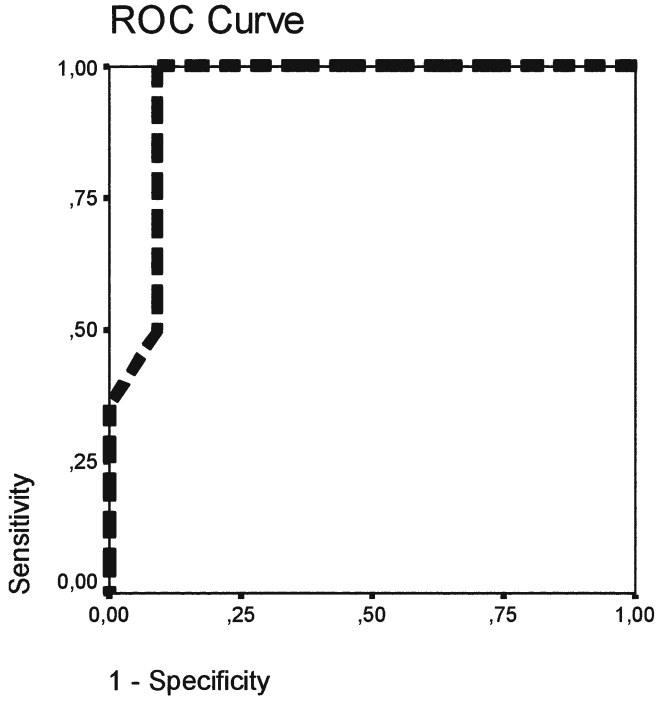

Fig. 3. Receiver operator characteristics (*ROC*) curve for the ability of BNP to predict an increased pulmonary capillary wedge pressure (>22 mmHg) in group A (patients with acutely decompensated heart failure). Area under the curve: 0.948; $P < 0.001$

In group A, BNP predicted increased PCWP (>22 mmHg) with an area under the ROC curve of 0.948 (standard error 0.052, $P < 0.001$ versus a true area of 0.500, Fig. 3). A cutoff BNP value of 842.5 pg/ml predicted increased PCWP with a sensitivity of 100% and a specificity of 91%. In group B, in contrast, the corresponding area under the ROC curve was 0.551 (standard error 0.118, $P = 0.663$ versus a true area of 0.500).

Discussion

The physiological definition of heart failure implies an inability of the heart to pump an adequate blood volume or to do so by an abnormally elevated filling pressure. It is well established that filling pressure elevation is associated with poor prognosis, and the dominant symptoms of heart failure usually reflect marked elevations in intracardiac filling pressures.[16,17] It becomes evident that left-sided filling pressures assessment has a crucial importance for a tailored therapy, based on hemodynamic data, in patients with heart failure.

The estimation of LVFP can be performed by both invasive and noninvasive means. Invasive measurement is performed by the insertion of balloon-tipped flow-directed catheters distal into the pulmonary artery. However, recent studies investigating the use of pulmonary catheters to guide patients' management during hospitalization for decompensation of heart failure did not reveal a sufficiently positive effect on patient mortality or length of hospitalization, suggesting that their use should not be a standard of care.[1–4] Moreover, complications resulting directly from invasive monitoring develop in 10% of patients, which raises concerns about their safety.[3]

The estimation of LVFP with reliable noninvasive modalities constitutes a major challenge in modern cardiology, and several methods have been proposed.[18–20] Among them, Doppler echocardiographic assessment of diastole has been widely applied for the noninvasive assessment of LVFP.[21] Recording of mitral inflow velocity pattern has provided useful information for determination of LVFP, with DT appearing to correlate better with PCWP.[18,22,23] However, transmitral flow velocity inflow depends on multiple inter-related factors such as left ventricular relaxation, compliance, and left atrial pressure.[5,18] To overcome these limitations, combination of the mitral flow velocity curves with other Doppler parameters has been applied.[5,6,18] In recent years, TDI of mitral annular motion has also been applied in the estimation of LVFP to correct for the influence of myocardial relaxation on transmitral flow.[5,18,20,24] Several investigations have shown that combining the mitral inflow with the mitral annular velocity measured by TDI into a ratio (E/Ea or the time interval between the onset of mitral E and annular early diastolic velocity) can predict LVFP.[6,18,25] When E/Ea is above 15, PCWP is usually >20 mmHg, whereas for E/Ea <8 LVFP are genererally low.[5,6] However, values between 8 and 15 are associated with a considerable variability of the corresponding LVFP and, therefore, E/Ea ratio in this zone cannot accurately predict LVFP.

It has been well established that BNP increases with the progression of heart failure and represents a cost-effective biomarker for the diagnosis and prognosis of heart failure.[26,27] In patients with chronic heart failure, BNP levels are strongly related to the TDI indexes, and constitute an independent predictor of death and cardiovascular events in both acute and chronic heart failure.[24,28] In a recent study concerning intensive care unit patients, both BNP and E/Ea

appeared more specific. In the same study, BNP appeared more accurate than E/Ea in patients without cardiac disease, while E/Ea appeared more accurate in patients with cardiac disease.[21]

In the present study, using PCWP invasively measured as the reference standard, we sought to assess whether BNP could predict LVFP in patients with systolic heart failure, either acutely decompensated (not in optimal treatment – group A) or well compensated (group B), and a nonpredictive E/Ea between 8 and 15. In group B patients we found no correlation between BNP and PCWP. This finding is consistent with previous observations that plasma BNP is not sufficiently sensitive or specific to detect significant systolic dysfunction in a stable population on long-term treatment for heart failure and that prolonged adequate treatment is reflected in falls in plasma BNP toward normal.[29] We wish to emphasize that BNP may not be either a clinically useful noninvasive marker of filling pressures in other clinical conditions, such as intensive care unit shock, especially in patients with impaired renal function.[30,31] On the contrary, in this group of patients transmitral DT correlated with PCWP. In acutely decompensated heart failure patients of group A, in contrast, BNP correlated with all the variables measured, including PCWP, DT, and SWS. Moreover, multivariate analysis showed that BNP was the only parameter that correlated significantly with PCWP. In accordance with our results, correlation of BNP with PCWP ($r = 0.79$) in patients under continuous hemodynamic recording was also shown by other investigators, who suggested that BNP might be effective in improving the in-hospital management of decompensated heart failure.[8] In another similar study conducted in an intensive care unit setting, the correlation between BNP and PCWP was lower ($r = 0.32$), which was attributed to the heterogeneity of the study population.[20] It should stated that the present observations concern patients with systolic heart failure and cannot be extrapolated to other common forms of heart failure such as diastolic heart failure.

In conclusion, BNP concentration is a simple, noninvasive tool to estimate LVFP in patients with acutely decompensated systolic heart failure in whom TDI E/Ea ratio is not conclusive. On the contrary, BNP does not appear to correlate with PCWP in stable patients under optimal medical therapy. In the latter patients BNP could be used to optimize medical treatment but estimation of PCWP is more accurately offered by Doppler indexes.

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