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Transcardiac gradients of N-terminal B-type natriuretic peptide in aortic valve stenosis

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Abstract

Background: Plasma B-type natriuretic peptide (BNP), as well as the N-terminal part of the prohormone (Nt-BNP), are frequently elevated in aortic valve stenosis (AS). Yet, their release from the heart into the circulation has never been directly studied in AS.
Aim: To assess the release of Nt-BNP in AS with focus on the identification of its main determinants.
Methods: We studied 49 adult patients undergoing preoperative cardiac catheterization for isolated AS. Blood was sampled from the aortic root and the coronary sinus for Nt-BNP determination by immunoassay.
Results: The mean (±S.E.) transcardiac Nt-BNP step-up averaged 79±53 pmol/l in 11 control patients free of structural heart disease, 75±32 pmol/l in 31 AS patients free of heart failure (HF), 236±62 pmol/l in 8 AS patients with diastolic HF (ejection fraction ≥50%, pulmonary wedge pressure >14 mm Hg) and 469±66 pmol/l in 7 AS patients with systolic HF (ejection fraction <50%, wedge pressure >14 mm Hg) ($p<0.001$). The transcardiac Nt-BNP gradient was independently associated with left ventricular (LV) end-diastolic pressure ($\beta=0.47$, $p<0.001$) and ejection fraction ($\beta=-0.29$, $p<0.019$) and with co-existent coronary artery disease ($\beta=0.23$, $p=0.050$).
Conclusion: LV diastolic and systolic dysfunction along with coronary artery disease are likely to be the key determinants of cardiac Nt-BNP release in AS. The transcardiac Nt-BNP gradient increases on average three-fold with the development of diastolic HF and six-fold in systolic HF.

Keywords: Natriuretic peptides; Aortic valve stenosis; Heart failure

1. Introduction

Natriuretic peptides, atrial and B-type, are circulating hormones synthesized in and released from the heart in response to atrial or ventricular wall stretch [1,2]. By promoting vasodilation and natriuresis and by counteracting neuroendocrine activation they protect the heart against pressure and volume overload. Easily measurable in samples of peripheral blood, B-type natriuretic peptide (BNP) in particular has been raised as a diagnostic tool in cardiology [2]. Elevated BNP helps identify heart failure (HF) [3], predict its prognosis [4]] and optimize its therapy [5]. As an alternative to BNP, the N-terminal moiety of the prohormone (Nt-BNP) can also be measured and may offer advantages due to its longer half-life and greater stability in the circulation [1,2,6].

Aortic valve stenosis (AS) produces left ventricular (LV) pressure overload and leads to progressive LV hypertrophy and filling impairment followed by diastolic and, ultimately, systolic HF. Earlier studies have shown that peripheral plasma BNP and Nt-BNP concentrations are elevated in AS [7–10], but there exist no direct data on the release of these agents from the heart in AS. We therefore measured the step-ups of plasma Nt-BNP from the aortic root to the coronary sinus in 49 patients undergoing cardiac catheterization for clinically isolated AS. Our main aim was to identify the key determinants of cardiac Nt-BNP secretion in AS. We found that both elevated LV end-diastolic pressure and reduced LV ejection fraction independently predicted high transcardiac Nt-BNP gradients and that there was an

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independent association also with angiographically significant coronary artery disease.

2. Methods

2.1. Study population

We considered for the present study all consecutive patients referred to our institution for a preoperative invasive study of AS between August 2000 and January 2003. The exclusion criteria were a history of myocardial infarction or otherwise confirmed coronary artery disease, more than mild aortic regurgitation, more than mild mitral valve disease, previous cardiac surgery, complicated diabetes and renal failure (serum creatinine >170 μmol/l). Of 137 patients undergoing cardiac catheterization and echocardiography as part of our research protocol, coronary sinus was accessible for blood sampling in 49 individuals. The clinical characteristics of these 49 patients, who constitute the present study population, are summarized in Table 1.

As a control group, we studied 11 patients who consented to sampling of blood from the aorta or femoral artery and from coronary sinus during an electrophysiologic study for supraventricular tachyarrhythmias (n=10) or unexplained syncope (n=1). History of arrhythmias aside, these patients were free of symptoms and signs of heart disease and had normal findings at echocardiography. Their demographics are included in Table 1. The study protocol was approved by the institutional ethics committee and all participants signed an informed consent document. The investigation conformed with the principles outlined in the Declaration of Helsinki.

Table 1
Clinical characteristics of the study population

	Patients with aortic stenosis (n=49)	Control patients (n=11)
Age, years	69±9	57±4*
Sex, male/female	25/24	6/5
Height, cm	167±10	172±10
Weight, kg	78±12	82±11
Body area, m^2	1.87±0.17	1.96±0.17
Serum creatinine >115 umol/l, n	6	0
NYHA class 1/2/3/4, n	2/30/16/1	all class 1
Rhythm at the time of study, n		
Sinus	45	11
Atrial fibrillation	4	0
Hypertension, n	25	2
Diabetes, n	3	0
Medication, n		
β-Adrenergic blocker	35	4
Diuretic	20	0
Angiotensin converting enzyme inhibitor	11	2
Spironolactone	2	0
Digoxin	1	0

NYHA=New York Heart Association.
* p<0.001.

2.2. Cardiac catheterizations

Cardiac catheterizations were made after an overnight fast using the femoral approach. After measuring pressures in the right heart and pulmonary artery, the coronary sinus was cannulated and blood was sampled from the aortic root and coronary sinus. The samples were not simultaneous but taken in rapid succession. The interval between the samples was determined by the aspiration time, which was about 30 s. Coronary angiography was made thereafter using standard selective techniques. Finally, the aortic valve was crossed for pressure recording during catheter pullback from the left ventricle into the aortic root. All pressures were measured using fluid-filled catheters with the zero reference level at the mid-axillary line. Cardiac output was measured by the Fick method. The aortic valve area was calculated by the Gorlin formula and indexed to body area. Coronary angiograms were analyzed visually. Luminal reductions exceeding 50% of the reference diameter were considered angiographically significant.

2.3. Echocardiography

The echocardiographic studies were done with an Acuson Sequoia scanner. The details and reproducibility of our methods to assess the aortic valve and the left ventricle have been reported earlier [11,12]. In brief, a parasternal M-mode recording was taken to measure the diameters of the cavity and walls of the left ventricle for calculation of LV mass [13] and mass index (mass/body area). The partition values for LV hypertrophy were set at 104 g/m^2 for women and 117 g/m^2 for men [14]. Relative LV wall thickness was calculated at end-diastole as (septal thickness+posterior wall thickness)/cavity diameter. Ejection fraction was determined from the apical four-chamber view using Simpson's formula. The transmitral flow velocities were recorded with pulsed Doppler to determine the early-to-late peak velocity ratio and the deceleration time (ms) of the early flow. Pulmonary venous flow was recorded with the sampling gate inside the right upper pulmonary vein. The systolic fraction (%) of the antegrade flow velocity integral [i.e., 100×systolic/(systolic+diastolic)] was determined. Pulsed and continuous wave Doppler were used to determine the aortic valve area index (valve area/body area) by the continuity equation [11]. The mean transvalvular pressure gradient was determined by the Bernoulli equation.

2.4. Measurement of Nt-BNP

The blood samples drawn from the aortic root and from the coronary sinus were taken into prechilled EDTA tubes,

Table 2
Heart rate, cardiac index and the characteristics of aortic valve obstruction in 49 patients with aortic stenosis

Measurement	Mean±S.D.	Range
Heart rate, bpm	62±11	41–94
Cardiac index, l/min/m^2	2.3±0.4	1.3–3.1
LV peak systolic pressure, mm Hg	202±31	152–270
Mean systolic LV-AO gradient, mm Hg[a]	44±16	10–78
Aortic valve area index, cm^2/m^{2a}	0.39±0.15	0.16–0.80

AO=aortic, LV=left ventricular.
[a] Based on cardiac catheterization in 45 patients and on Doppler echocardiography in 4 patients.

put on ice and centrifuged within 30 min. Plasma was stored at −80 °C and assayed later for Nt-BNP using a commercially available enzyme immunoassay (Biomedica, Vienna, Austria). The intra-assay coefficient of variation was 8.5% at a mean concentration of 935 pmol/l.

2.5. Statistical analysis

Comparisons across group means were done with Student's *t*-test or ANOVA. In case of grossly skewed data, we used the Kruskal–Wallis test. Univariate associations of the transcardiac Nt-BNP gradients with selected clinical data (Table 1) and with the invasive and non-invasive measurements (Tables 2 and 3) were assessed with Student's *t*-test or linear regression analysis. To identify the independent predictors of the gradients, we performed stepwise multiple linear regression analyses over the factors that were statistically significant ($p<0.05$) in univariate tests. The data are given as mean±S.E. unless indicated otherwise. All analyses were conducted using commercially available software (SYSTAT Version 10.1, Systat).

Table 3
Measurements of left ventricular structure and function in 49 patients with aortic stenosis

Measurement	Mean±S.D.	Range
Echocardiograpic measurements		
LV end-diastolic diameter, mm	48±6	37–64
Interventricular septal thickness, mm	15±2	11–19
Posterior wall thickness, mm	14±2	8–17
Relative wall thickness	0.57±0.11	0.29–0.83
LV mass index, g/m^2	154±38	83–236
LV ejection fraction, %[a]	59±13	28–80
Early-to-atrial transmitral peak velocity ratio	1.1±0.7	0.5–2.9
Deceleration time, ms	247±86	103–523
Systolic fraction of pulmonary venous flow, %	54±15	23–87
Invasive mesurements		
LV end-diastolic pressure, mm Hg[b]	21±9	3–44
Pulmonary capillary wedge pressure, mm Hg	13±6	4–30

LV=left ventricular.
[a] n=46.
[b] n=45.

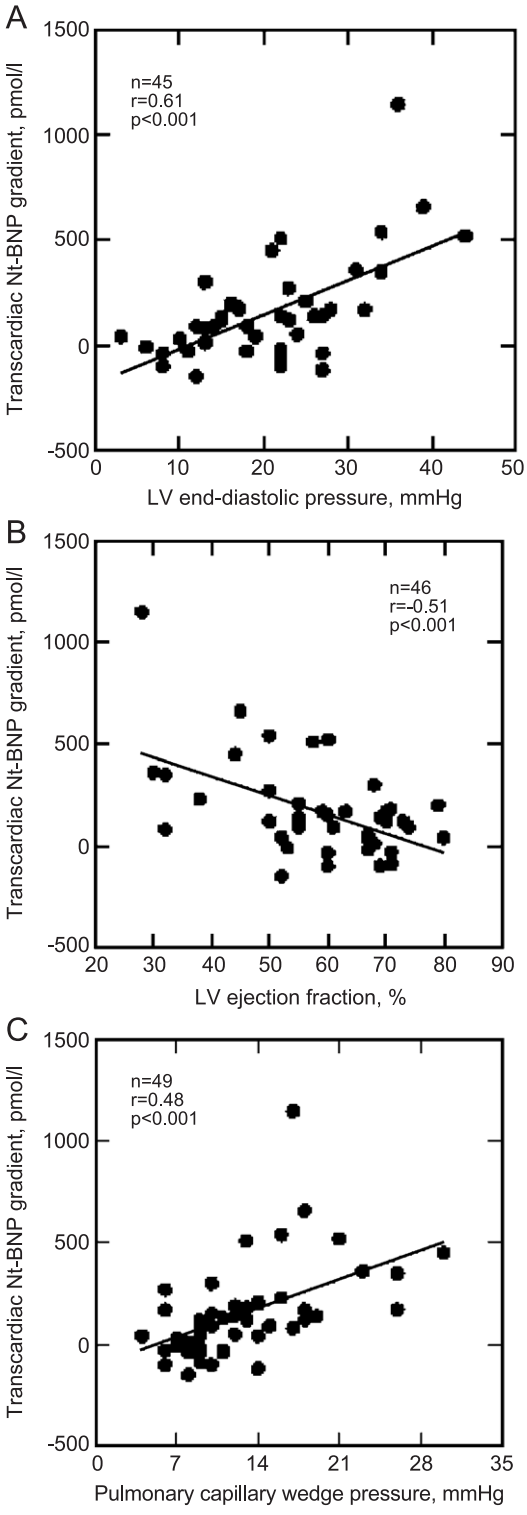

Fig. 1. Transcardiac plasma N-terminal brain natriuretic peptide (Nt-BNP) gradients in relation to left ventricular end-diastolic pressure (A), ejection fraction (B) and pulmonary wedge pressure (C) in patients with aortic stenosis.

3. Results

3.1. Invasive and non-invasive cardiac studies in patients with AS

The data pertinent to the severity of AS and the structure and function of the left ventricle are summarized in Tables 2 and 3. In patients in whom the aortic valve could not be crossed at catheterization (4 out of 49), the echocardiographic valve area and the mean transvalvular gradient were substituted for invasive measurements in all analyses. The aortic valve area index was <0.5 cm^2/m^2 in 40 patients as a sign of critical AS, 0.50–0.65 cm^2/m^2 in 7 patients and >0.65 cm^2/m^2 in 2 patients. It averaged 0.40±0.17 cm^2/m^2 in women vs. 0.38±0.12 cm^2/m^2 in men (p=NS). Forty-three out of 49 patients (88%) had LV hypertrophy by our sex-specific criteria (see Section 2). LV ejection fraction was subnormal (<50%) in 7 out of 46 patients (15%) with adequate recordings. Pulmonary capillary wedge pressure was elevated (>14 mm Hg) in 15 of 49 patients (31%). At coronary angiography, 17 patients (9 women and 8 men) had angiographically significant coronary artery obstructions. The remaining 32 patients had either mild changes or fully normal findings.

3.2. Transcardiac Nt-BNP gradients and their correlates

The median aortic Nt-BNP (range) was 1150 pmol/l (500–5440 pmol/l) in patients with AS vs. 430 pmol/l (170–630 pmol/l) in patients free of structural heart disease (p<0.001). The concentration rose from the aorta to the coronary sinus by a median of +120 pmol/l (−150 to +1150 pmol/l, p<0.001) in the AS group and by a median of +50 pmol/l (−80 to +210 pmol/l, p=0.028) in the control group.

In univariate analyses in patients with AS, transcardiac Nt-BNP gradient correlated statistically significantly with LV end-diastolic pressure, ejection fraction and pulmonary wedge pressure (Fig. 1 and Table 4). Less strong but still statistically significant associations were found with LV mass index and LV diastolic diameter as well as with the presence of coronary artery disease and with the mitral deceleration time (Table 4). On the other hand, the step-up of Nt-BNP was unrelated to age, sex and use of specific drugs and, more importantly, to all measures of AS severity including aortic valve area index, mean transvalvular pressure gradient and LV peak systolic pressure (data not shown). Nor was it related to either absolute or relative LV wall thickness.

In multivariate analysis, LV end-diastolic pressure, ejection fraction and coronary artery disease came out as independent predictors of the transcardiac Nt-BNP gradients (model 1 in Table 4). Since LV pressure measurements were missing in several patients, we made an alternative analysis substituting pulmonary wedge pressure for LV end-diastolic pressure as an independent variable. The result was a model, which encompassed a larger proportion of studied patients (46/49) and where the LV mass index also had independent influence (model 2 in Table 4). Models 1 and 2 explained 54% and 49%, respectively, of variation in the transcardiac plasma Nt-BNP gradient.

3.3. Transcardiac Nt-BNP gradients in systolic and diastolic HF due to AS

For the purposes of this work, the AS population was divided into 3 subgroups according to the presence and type of HF. Symptoms notwithstanding, 31 patients with ejection fraction ≥50% and pulmonary wedge pressure ≤14 mm Hg were considered to have “AS without HF”. The second group, “AS with diastolic HF”, consisted of eight patients with elevated pulmonary wedge pressure (>14 mm Hg) but normal ejection fraction. The third group, “AS with systolic HF”, consisted of seven patients with both subnormal ejection fraction (<50%) and elevated wedge pressure (>14 mm Hg). Fig. 2 compares the mean step-ups of plasma Nt-BNP from the aorta to the coronary sinus across the control group and the three subgroups of AS. The Nt-BNP gradient in AS without HF (75±32 pmol/l) was nearly

Table 4
Univariate and multivariate correlates of transcardiac gradient of plasma Nt-BNP in 49 patients with aortic stenosis

Variable	r	(p-value)	β-coefficient Model 1, n=42	(p-value)	β-coefficient Model 2, n=46[a]	(p-value)
LV end-diastolic diameter	0.35	(0.015)				
LV mass index	0.42	(0.003)			0.26	(0.046)
LV ejection fraction	−0.51	(<0.001)	−0.29	(0.019)	−0.27	(0.035)
LV end-diastolic pressure	0.61	(<0.001)	0.47	(<0.001)		
Pulmonary capillary wedge pressure	0.48	(<0.001)			0.26	(0.045)
Deceleration time	−0.30	(0.037)				
Coronary artery disease (0–2)[b]	0.39	(0.005)	0.23	(0.050)	0.25	(0.037)
			R^2=0.54	p<0.001	R^2=0.49	p<0.001

The data are correlation coefficients (r) and standardized regression coefficients (β-coefficient) from univariate and multivariate linear regression analyses, respectively, with the transcardiac plasma Nt-BNP gradient as the dependent variable. LV=left ventricular, R^2=squared multiple correlation coefficient (the explanatory power of the model).

[a] In model 2, pulmonary wedge pressure was substituted for LV end-diastolic pressure in the regression equation.

[b] Based on coronary angiography: 0=normal findings, 1=mild atherosclerotic changes, 2=luminal diameter reductions >50% in one or more arteries.

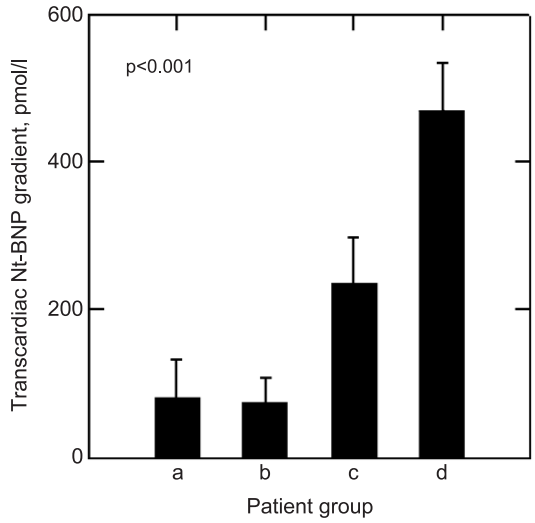

Fig. 2. Transcardiac plasma N-terminal brain natriuretic peptide (Nt-BNP) gradients (mean±S.E.) in control patients free of structural heart disease (a), and in patients with aortic stenosis without heart failure (b), with diastolic heart failure (c) and with systolic heart failure (d).

identical with the gradient in the control group (79±53 pmol/l) and much smaller than the gradients in the AS groups with diastolic (236±62 pmol/l, p=0.009) or systolic HF (469±66 pmol/l, p<0.001).

4. Discussion

We studied the hormonal activity of the heart in AS by measuring the step-up of plasma Nt-BNP from the aorta to the coronary sinus as an index of cardiac BNP secretion. We found that LV systolic and diastolic dysfunction (reduced ejection fraction and elevated end-diastolic pressure, respectively) were both important independent predictors of increased Nt-BNP gradients along with the presence of coronary artery disease. The degree of LV hypertrophy, instead, had little role independent of LV function and the degree of valve obstruction had no impact at all within the narrow spectrum of AS severity studied in our work.

The earlier studies on natriuretic peptides in AS involved only peripheral plasma BNP or Nt-BNP [7–10]. Because peripheral concentrations are strongly influenced by age, sex and renal function [15,16], they reflect Nt-BNP release from the heart less directly than the transcardiac concentration gradients. Yet, all earlier studies showed, as did ours, that circulating BNP and Nt-BNP are elevated in patients with AS relative to individuals free of heart disease. The correlates of plasma BNP or Nt-BNP varied from study to study but included LV end-systolic wall stress [7], aortic valve area [9,10], LV mass index [9,10], LV ejection fraction [9,10] and LV end-diastolic pressure [8,9].

In a study which involved patients with dilated cardiomyopathy instead of AS, Yasue et al. [17] measured the transcardiac step-ups of plasma BNP and found that they correlated with LV end-diastolic pressure (r=0.69) and ejection fraction (r=−0.74). Our results agree with these findings as well as with other clinical [18] and in vitro data [19] indicating that diastolic stretch of the LV myocardium is an important stimulus to the production of BNP by the human heart. In addition to mechanical stretch, a variety of neurohumoral factors (norepinephrine, angiotensin II, endothelin-1) can also influence myocardial BNP secretion [1]. These factors generally increase in activity with the development of LV systolic dysfunction. It is therefore possible that the independent inverse relation between ejection fraction and transcardiac NT-BNP gradient in our study reflected the effect of local neurohumoral activity increasing with decreasing systolic function.

According to our data, angiographically significant coronary artery disease also predicts increased gradients of plasma Nt-BNP from the aortic root to the coronary sinus. This suggests a contributory role for myocardial ischemia independent of LV function and accords with studies showing that transient ischemia increases plasma BNP concentration [20] and that elevated BNP is an independent predictor of stress-induced myocardial ischemia [21]. Furthermore, myocardial hypoxia per se can upregulate ventricular BNP gene expression [22].

Valve replacement is indicated in AS when the lesion is hemodynamically severe and produces symptoms. However, whether the patient has AS-related symptoms may not be easy to judge because some elderly individuals are well accustomed to physical inactivity, while others suffer from disabling non-cardiac diseases confusing the clinical assessment. A recent study from New Zealand [10] suggests that plasma Nt-BNP could discriminate between true symptoms and normal effort tolerance in AS. Our data indirectly support this observation by showing that the heart at least triples its secretion of Nt-BNP with the development of HF in AS. Prospective studies are needed to determine whether serial Nt-BNP measurements could help monitor disease progression and time for valve replacement.

An important limitation of our work is that we did not measure the flow of blood in the coronary sinus. Therefore, the true release of Nt-BNP from the heart per unit time (i.e. flow×arteriovenous difference) remained unknown. Because coronary blood flow is increased in LV hypertrophy, the mere arteriovenous Nt-BNP gradients may underestimate the differences in the Nt-BNP secretion between patients with and without LV hypertrophy. Thus, even AS patients free of heart failure probably had increased cardiac Nt-BNP secretion relative to the control group even though the mean transcardiac Nt-BNP gradients were nearly identical (see Fig. 2).

We conclude that transcardiac gradients of Nt-BNP are increased in severe AS in relation to the degree of diastolic and systolic LV dysfunction and to the presence of coronary artery disease. Relative to patients with AS free of HF, the Nt-BNP gradient is at least tripled in AS with diastolic HF and sextupled in AS with systolic HF.

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