Determinants and clinical significance of natriuretic peptides in hypertrophic cardiomyopathy

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Aims Atrial and brain natriuretic peptide levels closely reflect impaired left ventricular function in patients with heart failure. In the present study we assessed the determinants and the clinical significance of atrial and brain natriuretic peptide plasma levels in hypertrophic cardiomyopathy.

Methods and Results In 44 patients with hypertrophic cardiomyopathy (40 ± 15 years) we evaluated: (a) atrial and brain natriuretic peptide plasma levels; (b) left ventricular hypertrophy; (c) left ventricular ejection fraction; (d) transmirtal and pulmonary venous flow velocity patterns, and left atrial fractional shortening; (e) left ventricular outflow tract gradient; (f) maximal oxygen consumption. Left ventricular hypertrophy influenced only brain natriuretic peptide levels (r=0·32; P<0·05). Atrial and brain natriuretic peptide plasma levels did not correlate with left ventricular ejection fraction, but correlated with left ventricular outflow tract gradient (r=0·35, P<0·05; and r=0·40, P=0·022, respectively) and left atrial fractional shortening (r=−0·57; P<0·001, and r=−0·35; P<0·05, respectively). Atrial but not brain natriuretic peptide plasma levels were inversely related to maximal oxygen consumption (r=−0·35; P<0·05). By stepwise multiple regression analysis, left atrial fractional shortening and left ventricular outflow tract gradient were the only predictors of atrial and brain natriuretic peptide plasma levels, respectively.

Conclusions In hypertrophic cardiomyopathy, atrial natriuretic peptide plasma levels are mainly determined by diastolic function: this explains the relationship with exercise tolerance. In contrast, brain natriuretic peptide plasma levels are mainly determined by left ventricular outflow tract gradient.

Key Words: Cardiomyopathy, hypertrophy, natriuretic peptide, diastole.

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Introduction

Atrial and brain natriuretic peptides have diuretic, natriuretic, and vasodilator actions, and are involved in body fluid homeostasis and blood pressure control[1-2]. Atrial natriuretic peptide is produced mainly by atria[1-3], whereas the predominant source of brain natriuretic peptide appears to be cardiac ventricular tissue[4]. This dual natriuretic peptide system is activated in patients with impaired systolic function, in which increased secretion of atrial and brain natriuretic peptides closely reflect worsening left ventricular systolic function and progressive dilatation of left ventricle[5,6]. In patients with congestive heart failure, haemodynamic parameters associated with left ventricular dysfunction, such as pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, and left ventricular ejection fraction are related to atrial and brain natriuretic peptides[6-8]. This dual natriuretic peptide system is also activated in hypertrophic cardiomyopathy, a cardiac disease characterized by primary myocardial hypertrophy, normal or supernormal left ventricular systolic function, left ventricular diastolic dysfunction, and, in about 25% of patients, by left ventricular outflow tract obstruction[9]. The enhanced production of natriuretic peptides in hypertrophic cardiomyopathy has been related to left ventricular outflow tract obstruction, left
ventricular hypertrophy, and left ventricular diastolic dysfunction[10–13]. However, no previous study has systematically assessed the influence of structural and functional factors stimulating atrial and brain natriuretic peptide secretion in hypertrophic cardiomyopathy. Furthermore, to our knowledge, there are no available data which correlate clinical status with atrial and brain natriuretic peptide plasma levels in hypertrophic cardiomyopathy.

The present study was designed to assess the pathophysiological role and the clinical significance of the natriuretic peptide system in hypertrophic cardiomyopathy.

Methods

Study population

The study included 44 patients with hypertrophic cardiomyopathy (32 men and 12 women) aged 40 ± 15 years (range 16–68 years). The diagnosis of hypertrophic cardiomyopathy was based upon M-mode and two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle in absence of any identifiable causes of secondary hypertrophy[9]. All patients were in sinus rhythm and none had any conduction abnormalities or left or right bundle branch block. Enrolment criteria included an excellent acoustic window to allow reliable quantitative echocardiography.

At the time of the study, patients were not taking drugs: in particular, calcium antagonists were withdrawn at least five half-lives before the study and beta-blockers were titrated off so that five half-lives elapsed before the study protocol. This population’s data are part of another study[13].

Blood sampling

Patients fasted overnight. Patients assumed a supine position for at least 30 min before blood sampling. Peripheral venous blood samples were taken slowly from the ante-cubital vein and transferred to chilled disposable tubes containing 2-sodium-ethylenediaminetetraacetic acid. Blood samples were placed immediately on ice and promptly centrifuged at 4 °C, and aliquots of plasma were immediately stored at −80 °C until the assay.

Measurement of atrial and brain natriuretic peptide plasma levels

Atrial and brain natriuretic peptides were extracted from plasma with SEP-PACK C18 Cartridges (Amersham International Ltd). Plasma immunoreactive atrial natriuretic peptide levels were determined by radioimmunoassay as previously described by our laboratory[14]. Intra-assay and inter-assay variation coefficients were 6.6% and 9.9%, respectively. The radioimmunoassay sensitivity was 1 femtomole per tube. Plasma brain natriuretic peptide levels were measured using an anti-hBNP-32 antibody (Peninsula Laboratories) as previously described by our laboratory[15]. The minimal detectable quantity in the radioimmunoassay was 0.5 femtomole per tube. Intra- and inter-assay coefficient variations were 5.8% and 14%, respectively.

Echocardiography

Echocardiography and Doppler ultrasound examinations were performed using a Hewlett-Packard imaging system (77030A Sonos 1000) with a combined 3.5 MHz imaging/2.5 MHz Doppler transducer. Images were stored on a videotape recorder for analysis. All patients underwent echocardiographic study 30 min before the cardiopulmonary exercise test.

Two-dimensional echocardiography was performed using standard cross-sectional planes. The extent of left ventricular hypertrophy (i.e. hypertrophy score index) was calculated from the short-axis view by dividing the left ventricular wall into four segments (anterior septum, posterior septum, lateral free wall, posterior free wall) both at the level of mitral valve and papillary muscle, and by adding the maximal wall thickness measured (at either the mitral valve or papillary muscle level) in each of the four ventricular segments[9,10]. The distribution of hypertrophy was assessed according to Maron’s classification[9]. Left ventricular ejection fraction was assessed by the area–length method.

Left ventricular diastolic function was assessed by two echocardiographic methods, as previously described[17]. From the left atrial M-mode echogram, left atrial fractional shortening (used as an index of passive diastolic phase), and the slope of the posterior aortic wall displacement during early left atrial emptying (i.e. a reliable index of left ventricular isovolumetric relaxation) were calculated as previously described in detail[17]. Briefly, two left atrial anteroposterior diameters (LAD) were measured: (1) maximum, at ventricular end-systole (at the end of the electrocardiographic T wave; LADmax, mm), and (2) minimum, at the end of atrial contraction (measured at the peak of the electrocardiographic R wave; LADmin, mm). Left atrial fractional shortening was calculated as [(LADmax–LADmin)/LADmax]·100. We previously demonstrated that left atrial fractional shortening is lower in patients with higher left ventricular end-diastolic pressure and increased left ventricular chamber stiffness. The slope of posterior aortic wall displacement during early left atrial emptying is lower in patients with impaired left ventricular isovolumetric relaxation[17].

Diastolic flow velocity at the left ventricular inflow tract was determined as previously reported[13,17]. The following variables were measured: peak flow velocity in early diastole (E), and during atrial contraction (A), and their ratio (E/A ratio); deceleration time of early diastolic flow velocity, and duration of the A wave.
Pulmonary venous flow velocity was obtained in the apical four-chamber view by placing the sample volume 0.5 to 1 cm into the upper right pulmonary vein. The following variables were measured: peak velocity of systolic (S), diastolic (D), and retrograde (R) flow velocities, S/D ratio, R duration, and the systolic filling fraction (i.e. the ratio of systolic to the sum of systolic and diastolic velocity integrals). In addition, the difference in duration between retrograde pulmonary venous flow and forward mitral flow during atrial systole A was calculated. In the case of biphasic systolic flow, the maximal velocity was measured on the tallest of the two peaks. The following variables were considered as indexes of abnormal diastolic function: S/D ratio < 1; systolic filling fraction < 0.40; peak of R velocity flow > 35 cm.s⁻¹, a positive difference in duration between the retrograde pulmonary venous flow and the mitral A wave. Four different patterns of left ventricular filling were considered, depending on the E/A ratio, the E wave deceleration time, and the pulmonary venous flow velocity indexes of abnormal diastolic function: (1) normal pattern (i.e. E/A ratio between 1 and 2, E wave deceleration time between 150 and 250 ms, and normal pulmonary venous flow velocity indexes); (2) pattern of prolonged relaxation (i.e. E/A ratio < 1 and E wave deceleration time > 250 ms), that indicates an impairment in the early, active phase of diastole (relaxation); (3) pseudonormal pattern (i.e. E/A ratio between 1 and 2, E wave deceleration time between 150 and 250 ms, and abnormality in one or more pulmonary venous flow velocity indexes of diastolic dysfunction), that indicates an intermediate stage of diastolic impairment, when the E wave increases due to the rise in left atrial pressure and the E/A ratio appears to be back to normal; and (4) pattern of restrictive filling (E/A ratio ≥ 2 and E wave deceleration time < 150 ms), that indicates an impairment in the late, passive phase of diastole (stiffness). A positive difference > 30 ms in duration between the pulmonary venous flow retrograde and the mitral A wave has been proposed as an index of high left ventricular end-diastolic pressure.

The presence of a left ventricular outflow tract gradient was evaluated with continuous-wave Doppler, using the simplified Bernoulli equation (AP = 4v², where P is pressure and v is flow velocity). Care was taken to distinguish ejection velocity from the mitral regurgitation jet.

The presence and severity of mitral regurgitation was determined by measuring the regurgitation jet area by colour Doppler, and by evaluating the presence of a backward pulmonary venous systolic flow.

Cardiopulmonary exercise test

All patients underwent symptom-limited cycloergometer exercise soon after the echocardiographic study. Patients were connected with a 2001 instrument (Medical Graphics, St. Paul, MN, U.S.A.) to analyse breathing patterns and to measure oxygen uptake, and carbon dioxide release. The electrocardiogram was continuously monitored. Blood pressure was measured every 2 min by the auscultatory method. All patients exercised at constant speed (60 rpm) for 3 min; the workload was then increased by 1 watt every 3 s (ramp protocol) until patients complained of either shortness of breath or fatigue. Resting oxygen consumption was determined as the average of 2 min with the subject sitting on the cycloergometer before starting exercise. Maximal oxygen consumption was defined as the 10 s averaged peak exercise value of oxygen consumption. Values of maximal oxygen consumption ≤ 20 ml.kg⁻¹.min⁻¹ were considered abnormal.

Statistical analysis

All echocardiographic measurements were performed by averaging three consecutive cardiac cycles. Data were expressed as the mean ± 1 standard deviation. All statistical calculations were performed using SPSS for Windows, Release 7.5. Because the distribution of atrial and brain natriuretic peptides did not appear to be normal, a Shapiro–Wilks test for normality was performed, and data were analysed by the Mann–Whitney U-test and the Kruskal–Wallis H test. Chi-square analysis was used to test differences in categorical variables.

To determine which clinical and echocardiographic parameters best describe plasma atrial and brain natriuretic peptide levels, the values were transformed into a natural logarithm to overcome the problem of the non-normal distribution; then stepwise multiple linear regression analysis was used, where lnANP and lnBNP were put in turn as independent variables. Linear regression involving atrial and brain natriuretic peptides were also performed using the natural logarithm data. A P value of less than 0.05 was considered significant.

Results

Patients’ characteristics

Table 1 outlines the principal clinical and echocardiographic characteristics of our patient population. Averaged septal thickness was 21 ± 5 (range 15–32) mm. According to Maron’s classification, five patients were ranked as type I, 30 as type II, and nine as type III. Mitral regurgitation was identified in 21 patients, and classified trivial in 19, and moderate in two patients. No patients had pulmonary systolic backward flow. The E/A ratio was < 1 in 14 patients, and ≥ 2 in seven patients. E wave deceleration time was < 150 ms in three patients, and 150–250 ms in 14. The difference in duration between the pulmonary R wave and mitral A wave was > 30 ms in 12 patients. The pulmonary S/D ratio was low (< 1) in 11 patients, and systolic filling fraction was < 0.40 in four patients. The pulmonary R wave peak was high (> 35 cm.s⁻¹) in nine patients.
Plasma concentration of natriuretic peptides

For technical reasons, plasma atrial and brain natriuretic peptide concentrations were not assessed in six, and two patients, respectively. Plasma atrial and brain natriuretic peptide levels were 87 ± 59 (range 22–232) pg. ml⁻¹, and 54 ± 43 (range 3–155) pg. ml⁻¹, respectively. The distribution of plasma natriuretic peptides was not normal, as they were skewed towards low values (atrial natriuretic peptides: \( P=0.010 \), brain natriuretic peptides: \( P=0.031 \) by the Shapiro–Wilk test).

Morphological parameters and natriuretic peptides

The natural logarithm of plasma natriuretic peptide levels correlated with left atrial diameters (both maximum and minimum), but not with left ventricular dimensions (Table 2). The distribution of left ventricular hypertrophy, assessed by Maron’s classification did not influence the plasma levels of either lnANP (\( P=0.64 \)) or lnBNP (\( P=0.07 \)). The extent of left ventricular hypertrophy (i.e. hypertrophy score index) correlated only with plasma lnBNP levels (Table 2).

Left ventricular systolic function and natriuretic peptides

Left ventricular systolic function, assessed as both left ventricular ejection fraction, and left ventricular fractional shortening, did not affect plasma lnANP and lnBNP concentrations (Table 2).

Left ventricular diastolic function and natriuretic peptides

Left atrial fractional shortening was inversely correlated with both lnANP and lnBNP levels (Table 2; Fig. 1). The slope of posterior aortic wall displacement during early atrial emptying correlated with lnANP, but not lnBNP (Table 2). The distribution of the four Doppler-derived diastolic patterns (i.e. normal, abnormal relaxation, pseudonormal, and restrictive), are summarized in Table 1. Plasma atrial and brain natriuretic peptide levels were not significantly different among the four Doppler patterns (atrial natriuretic peptides: \( P=1.0 \), brain natriuretic peptides: \( P=0.21 \)). Atrial natriuretic peptide plasma levels were 80 ± 51 pg. ml⁻¹ in patients without and 104 ± 75 pg. ml⁻¹ in patients with a positive difference >30 ms in duration between the pulmonary venous flow retrograde and the mitral A wave (\( P=0.57 \)). Brain natriuretic peptide plasma levels were 54 ± 43 pg. ml⁻¹ in patients without and 54 ± 44 pg. ml⁻¹ in patients with a positive difference >30 ms in duration between the pulmonary venous flow retrograde and the mitral A wave (\( P=0.91 \)).

Left ventricular outflow tract obstruction

Nine of the 44 patients (20%) had a resting left ventricular outflow tract gradient ≥30 mmHg. Patients with the obstructive form of hypertrophic cardiomyopathy had higher plasma levels of atrial and brain natriuretic peptides than patients without a resting left ventricular outflow tract gradient (atrial natriuretic peptides: 143 ± 79 vs 71 ± 41 pg. ml⁻¹, \( P=0.022 \); brain natriuretic peptides: 51 pg. ml⁻¹ vs 21 pg. ml⁻¹, \( P=0.021 \)).
peptides: 90 ± 48 vs 45 ± 38 pg . ml⁻¹, P=0·015, respectively). Furthermore, by univariate linear regression analysis, the left ventricular outflow tract gradient directly influenced both lnBNP and lnANP (Table 2; Fig. 2).

Clinical and functional indexes

Age did not correlate with either atrial or brain natriuretic peptide levels (Table 2). The cardiopulmonary exercise test was terminated by shortness of breath or fatigue, or both, in all patients; no patients had angina, ST depression, or arrhythmia. Exercise time was 9 ± 2 (range 5–13) min. Heart rate increased from 77 ± 16 at rest to 138 ± 22 beats . m⁻¹ at peak exercise. Three patients had exercise-induced hypotension: in none of them, however, was the exercise test prematurely interrupted because systolic blood pressure never fell below 100 mmHg. The mean value of maximal oxygen consumption was 25 ± 8 (ranging from 14 to 45) ml . kg⁻¹ min⁻¹; 14 (33%) patients reached a subnormal maximal oxygen consumption (i.e. ≤ 20 ml . kg⁻¹ min⁻¹). The mean value of the anaerobic threshold was 14 ± 5 (ranging from 6 to 33) ml . kg⁻¹ min⁻¹. Plasma atrial natriuretic peptide levels were significantly higher in patients with reduced than in those with normal exercise tolerance (122 ± 72 vs 70 ± 44 pg . ml⁻¹, P=0·037). In contrast, plasma brain natriuretic peptide levels were not statistically different in the two groups (53 ± 44 vs 55 ± 42 pg . ml⁻¹, P=0·89). Furthermore, by univariate linear regression analysis, lnANP and not lnBNP correlated with maximal oxygen consumption (Table 2; Fig. 3).

By stepwise multiple linear regression analysis, the only predictor of plasma lnANP was left atrial fractional shortening (r=−0·57; P<0·001; F=16·411), and the

Discussion

Left ventricular hypertrophy and natriuretic peptides

In the present study, the distribution of left ventricular hypertrophy did not correlate with either atrial or brain natriuretic peptide plasma levels, whereas the severity of left ventricular hypertrophy influenced only plasma brain natriuretic peptide levels.

The influence of left ventricular hypertrophy on bio-synthesis, secretion, and plasma levels of brain natriuretic peptide in hypertrophic cardiomyopathy has been previously reported. Nishigaki et al. reported that in hypertrophic cardiomyopathy the immunohistochemical expression of ventricular brain natriuretic peptide has a significant relationship with hypertrophy of myocytes, besides disarray and fibrosis. In contrast, plasma levels of atrial natriuretic peptides are not affected by the distribution and the severity of left ventricular hypertrophy. Hasegawa et al. reported that in hypertrophic cardiomyopathy, atrial natriuretic peptides, although expressed in the hypertrophied ventricle, are secreted predominantly from atria.

Left ventricular systolic function and natriuretic peptides

Atrial and brain natriuretic peptide levels have been indicated as markers of the severity of left ventricular
studies from our group\cite{15,23,24} in patients with dilated NYHA functional classes. In particular, in previous failure, closely re

and brain natriuretic peptide plasma levels are elevated /p1

the more advanced stages (44 pg . ml\(^{-1}\) vs 13 pg . ml\(^{-1}\) in controls) and continued to increase in

the more advanced stages (44 pg . ml\(^{-1}\), 105 pg . ml\(^{-1}\), 242 pg . ml\(^{-1}\) on average in NYHA classes II, III and IV, respectively). Brain natriuretic peptide levels consistently doubled in patients with dilated cardiomyopathy with each step across NYHA classes, closely following deterioration in left ventricular function. In our current study in hypertrophic cardiomyopathy, left ventricular systolic function was normal in all patients and was not related to plasma atrial and brain natriuretic peptide levels. This may explain the lack of correlation between systolic function and atrial and brain natriuretic peptides, as these peptides are influenced by altered haemodynamics associated with poor systolic function.

**Left ventricular diastolic function and natriuretic peptides**

Abnormalities in left ventricular relaxation, filling, and compliance are common in patients with hypertrophic cardiomyopathy\cite{9,19}. Our study demonstrates that atrial and brain natriuretic peptide levels are inversely related to left atrial fractional shortening (i.e. a reliable, non-invasive index of left ventricular end-diastolic pressure\cite{27}), while the slope of the posterior aortic wall
during early left atrial emptying (i.e. a reliable index of left ventricular isovolumetric relaxation\cite{17}) influences atrial natriuretic peptide levels only. Moreover, by stepwise multiple linear regression analysis, left atrial fractional shortening is the only determinant of atrial natriuretic peptide levels. These findings are consistent with previous studies that demonstrated a correlation between atrial and brain natriuretic peptides and left ventricular end-diastolic pressure\cite{5,8,12}. Furthermore, Burnett et al. found that only left ventricular end-diastolic pressure was an independent predictor of atrial natriuretic peptides among a number of haemodynamic parameters\cite{23}. In contrast, there is no correlation between atrial and brain natriuretic peptide levels and Doppler-derived left ventricular diastolic filling patterns. Analysis of the left ventricular filling pattern using pulsed-Doppler echocardiography, by the evaluation of both transmitral and pulmonary vein flow velocity patterns, has been widely used in hypertrophic cardiomyopathy but little evidence exists that it reflects true diastolic function as evaluated invasively\cite{17,26}.

**Left ventricular outflow tract gradient and natriuretic peptides**

Left ventricular outflow tract gradient directly influenced both atrial and brain natriuretic peptide levels. In particular, left ventricular outflow tract gradient was the only determinant of brain natriuretic peptide levels in our patient population. The influence of left ventricular outflow tract gradient on natriuretic peptides in hypertrophic cardiomyopathy has been reported previously\cite{10,12}. Nishigaki et al. proposed plasma brain natriuretic peptide elevation as a special feature that can be used to distinguish obstructive from non-obstructive hypertrophic cardiomyopathy\cite{10}.

**Possible mechanisms of abnormal elevation of plasma natriuretic peptide levels in hypertrophic cardiomyopathy**

The mechanisms controlling the release of atrial and brain natriuretic peptides remain uncertain despite extensive investigation. Pressure–stretch release coupling mechanisms have been identified as the principal stimulus of both atrial and brain natriuretic peptide secretion.

**Plasma atrial natriuretic peptide levels (Fig. 4)**

It is generally accepted that atrial natriuretic peptide is produced mainly in the atria\cite{5}; in particular, diastolic dysfunction seems to be the principal stimulus of atrial natriuretic peptide secretion in hypertrophic cardiomyopathy. Diastolic dysfunction may stimulate atrial natriuretic peptide secretion by increasing atrial wall stretch\cite{27,28}. Edwards et al. demonstrated that the
The principal stimulus for atrial natriuretic peptide release from the atria is mechanical stretch (or atrial transmural pressure) and not increased intracavitary atrial pressure[27]. In keeping with these observations, the higher plasma atrial natriuretic peptide levels observed in patients with lower left atrial fractional shortening (i.e. higher left ventricular end-diastolic pressure) are probably due to the increase in atrial pressure and, therefore, stretching of the myocardium. In other words, left ventricular diastolic dysfunction (by increasing atrial pressure and, thus, a rise in left atrial pressure) seems to be the principal stimulus for atrial natriuretic peptide secretion. The influence of left ventricular outflow tract obstruction may be both direct (by stimulating ventricular release) and indirect (by inducing mitral regurgitation, and thus a rise in left atrial pressure). Furthermore, it is possible that a high level of atrial natriuretic peptide may reduce preload and afterload, subsequently exacerbating left ventricular obstruction.

**Figure 4**
Factors influencing atrial natriuretic peptide plasma levels in hypertrophic cardiomyopathy. Left ventricular diastolic function and left ventricular outflow tract obstruction, but not left ventricular hypertrophy, are involved in the abnormal elevation of plasma atrial natriuretic peptide levels in hypertrophic cardiomyopathy. In particular, diastolic dysfunction (by increasing left atrial stretch) seems to be the principal stimulus of atrial natriuretic peptide secretion. The influence of left ventricular outflow tract obstruction may be both direct (by stimulating ventricular release) and indirect (by inducing mitral regurgitation, and thus a rise in left atrial pressure). Furthermore, it is possible that a high level of atrial natriuretic peptide may reduce preload and afterload, subsequently exacerbating left ventricular obstruction.

Plasma brain natriuretic peptide levels (Fig. 5)
A major finding of the present study is that plasma brain natriuretic peptide levels are related to left ventricular outflow tract gradient, left ventricular diastolic dysfunction, and severity of left ventricular hypertrophy. In particular, left ventricular outflow tract obstruction (by increasing left ventricular systolic wall stress) seems to be the principal stimulus for brain natriuretic peptide secretion. Furthermore, it is possible that a high level of brain natriuretic peptide may reduce preload and afterload, subsequently exacerbating left ventricular obstruction.

**Figure 5**
Factors influencing brain natriuretic peptide plasma levels in hypertrophic cardiomyopathy. Left ventricular outflow tract obstruction, left ventricular diastolic function and severity of left ventricular hypertrophy are involved in the abnormal elevation of the plasma brain natriuretic peptide levels in hypertrophic cardiomyopathy. In particular, the increased left ventricular systolic wall stress (induced by left ventricular outflow tract obstruction) seems to be the principal stimulus of brain natriuretic peptide secretion. Furthermore, it is possible that a high level of brain natriuretic peptide may reduce preload and afterload, subsequently exacerbating left ventricular obstruction.
Exercise capacity and natriuretic peptides

In the present study, we found a significant inverse correlation between plasma atrial natriuretic peptide level and exercise tolerance (Fig. 3). Some studies demonstrated that left ventricular diastolic dysfunction is the principal determinant of symptoms (such as dyspnea) and exercise capacity in patients with hypertrophic cardiomyopathy. Since left atrial fractional shortening is the main determinant of plasma atrial natriuretic peptide levels, one may speculate that the reduced exercise tolerance in patients with higher atrial natriuretic peptide levels is the consequence of left ventricular diastolic dysfunction. This provides further evidence to our previous report suggesting that left atrial fractional shortening (i.e. a reliable non-invasive index of left ventricular diastolic passive properties) is a predictor of exercise capacity in patients with hypertrophic cardiomyopathy. With this in mind, the lack of correlation of brain natriuretic peptide levels with exercise tolerance could be explained by the minor influence of diastolic function on brain natriuretic peptide secretion.

Limitations of the study

Left ventricular function has been assessed non-invasively. In particular, left ventricular diastolic function was determined by the analysis of a complex interaction of multiple variables which include properties intrinsic to the left ventricle such as elasticity, relaxation rate, contractile state, and properties extrinsic to the left ventricle such as blood volume, pericardium, and right ventricular function. Pressure/stretch release coupling may not be the only mechanism involved in the activation of atrial and brain natriuretic peptide genes. In fact, local and circulating angiotensin II and endothelin have been shown to induce ANP and brain natriuretic peptide transcription.

References
