Enhanced brain natriuretic peptide response to peak exercise in heart transplant recipients

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Enhanced brain natriuretic peptide response to peak exercise in heart transplant recipients. J. Appl. Physiol. 85(6): 2270–2276, 1998.—We investigated the atrial (ANP) and brain natriuretic peptides (BNP), catecholamines, heart rate, and blood pressure responses to graded upright maximal cycling exercise of eight matched healthy subjects and cardiac-denervated heart transplant recipients (HTR). Baseline heart rate and diastolic blood pressure, together with ANP (15.2 ± 3.7 vs. 4.4 ± 0.8 pmol/l; P < 0.01) and BNP (14.3 ± 2.6 vs. 7.4 ± 0.6 pmol/l; P < 0.01), were elevated in HTR, but catecholamine levels were similar in both groups. Peak exercise O2 uptake and heart rate were lower in HTR. Exercise-induced maximal ANP increase was similar in both groups (167 ± 34 vs. 216 ± 47%). Enhanced BNP increase was significant only in HTR (37 ± 8 vs. 16 ± 8%; P < 0.05). Similar norepinephrine but lower peak epinephrine levels were observed in HTR. ANP and heart rate changes from rest to 75% peak exercise were negatively correlated (r = −0.76, P < 0.05), and BNP increase was correlated with left ventricular mass index (r = 0.83, P < 0.01) after heart transplantation. Although ANP increase was not exaggerated, these data support the idea that the chronotropic limitation secondary to sinus node denervation might stimulate ANP release during early exercise in HTR. Furthermore, the BNP response to maximal exercise, which is related to the left ventricular mass index of HTR, is enhanced after heart transplantation.

catecholamines; echocardiographic data; hemodynamics; oxygen uptake

Atrial and brain natriuretic peptides (ANP and BNP, respectively) are thought to play a major role in blood pressure and fluid homeostasis, protecting the body against volume and pressure overloads. Both cardiac hormones, constituting a dual cardiac natriuretic system, have well-recognized natriuretic, diuretic, and hypotensive properties, and BNP appears to act additionally or in synergy with ANP. Furthermore, BNP has a direct positive lusitropic effect (3, 6, 8).

During dynamic exercise, circulatory homeostasis is challenged and body fluid- and pressure-regulating hormone secretion is enhanced. In particular, increased atrial stretch, secondary to increased venous return, greatly stimulates ANP secretion during and immediately after exercise in normal humans (7, 9, 25, 32). In contrast, there is generally no exercise-induced plasma BNP change in normal subjects, and the stimulus for BNP release is not yet clearly identified (26, 29).

Heart transplantation generally normalizes the left ventricular systolic function, but the transplanted heart is characterized by its diastolic dysfunction, which is often associated with cardiac hypertrophy. Furthermore, the transplantation procedure results in cardiac denervation. These particularities may modify both the hemodynamic and neurohormonal responses of heart transplant recipients (HTR) to maximal exercise (18, 20, 31). Thus, despite the fact that cardiac innervation is not needed for ANP release, some studies suggested that an enhanced exercise-induced circulating ANP increase after heart transplantation may be ascribed to cardiac denervation (2, 10, 33). However, cardiac denervation is only partial after heart transplantation, and a clear relationship between ANP increase during exercise and cardiac denervation remains to be shown.

To date, the BNP response to exercise after heart transplantation is unknown. Because it has been recently demonstrated that BNP infusion causes beneficial hemodynamic and neurohormonal effects during exercise in patients with isolated diastolic heart failure (6), it may be interesting to determine the effect of exercise on BNP in HTR and to investigate the relationships between this cardiac hormone increase and factors known to affect the heart's diastolic function.

The aim of this study was therefore to determine simultaneously the ANP and BNP responses to maximal exercise in cardiac-denervated HTR and to investigate the factors modulating their release. We hypothesized that an early delay in heart rate increase, secondary to sinus node denervation, may enhance the ANP secretion of HTR. Furthermore, we tested the hypothesis of an exercise-induced exaggerated BNP increase, likely related to an increased left ventricular mass index (LVMI) after heart transplantation.

METHODS

Study population. Sixteen men, eight healthy controls and eight HTR, matched for age and weight, gave their informed consent and participated in this study, which was approved by the University Review Board for Human studies. All subjects were in sinus rhythm and were cardiac-symptom free. All HTR, who were free of rejection, received triple immunosuppressive therapy with prednisolone (9.4 ± 1.5 mg/day), cyclosporine with total blood residual level at 168 ± 18 ng/ml, and azathioprine (23.4 ± 6.9 mg/day). Other medications included calcium antagonists (n = 1), nitrate (n = 2), angiotensin-conversion inhibitors (n = 2), and/or furosemide (n = 3) in HTR. Care was taken to avoid medica-

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tion limiting the chronotropic response so that a possible delay in heart rate increase might be mainly ascribed to sinus node denervation of the transplanted patients. None of the sedentary control subjects was taking medication.

Exercise protocol. To minimize the effect of exercise duration, temperature, and circadian variations on hormonal secretions, room temperature was kept constant, and all exercise tests took place on the early afternoon. During a 45-min resting period, a 20-gauge catheter was inserted into an antecubital vein for blood withdrawal. Then, subjects performed a graded exercise test in the upright position, by using an electronically braked bicycle ergometer (Medifit 1000S) and a breath-by-breath metabolic measurement chart (Medisoft). The initial workload was 20 W during 3 min, with maximal exercise being thereafter performed by both controls and HTR until exhaustion. The workload was increased every minute to reach the maximal tolerated power, previously determined, in 10 min. The following recovery period lasted 30 min.

Hemodynamic and respiratory parameters. Heart rate was measured with an electrocardiographic recorder (Schiller), and systemic blood pressure was determined noninvasively with the oscilometric method by using an automatic tensiometer (Critikon, Paris, France). Echographic data were obtained at rest, with the subject in left decubitus position, by using an Advanced Technology Laboratories Ultramark 9 echo Doppler and a 2.25-MHZ transducer. Left ventricular fractional shortening, interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), and left ventricular diameter (LVD) were determined by using the left parasternal long axis view. From these parameters, LVM was then calculated according to the usual equation: LVM = 1.04 [(IVST + LVPWT + LVD)^3 – LVD^3] – 13.6/body area.

Oxygen consumption was determined from a breath-by-breath measurement chart (Medisoft Partnair 5400, Dyn’air, France).

Biological and hormonal determinations. Venous blood samples were withdrawn at rest, in the last minute of the submaximal workload corresponding to ~75% of peak working capacity (74.2 ± 3.4 vs. 78.4 ± 4.2% in HTR and controls, respectively), at peak exercise, and after 10 and 30 min of recovery.

Serum samples were analyzed for Na⁺, K⁺, and osmolality by using the freezing-point depression method. Rest and peak exercise hematocrit was determined to estimate plasma volume change.

Both plasma ANP and BNP were determined by radioimmunoassay, after extraction on Sep Pak C₁₈ cartridges (Waters, Milford, MA). Circulating ANP was determined by using kits from Amersham (Buckinghamshire, UK). The intra-assay coefficient of variation for duplicate samples averaged 8% for levels >16 pmol/l and 12% for levels <16 pmol/l. The sensitivity of the assay was 2 pmol/l. Circulating BNP was determined by using kits from Peninsula Laboratories (Belmont, CA). The intra-assay coefficient of variation for duplicate samples averaged 6% for levels >23 pmol/l, 8% for levels between 23 and 9 pmol/l, and 10% for levels <9 pmol/l. The sensitivity of the assay was 2 pmol/l. Plasma catecholamines, norepinephrine, and epinephrine, were determined by high-performance liquid chromatography and electrochemical detection (Waters).

Statistical analysis. All the results are expressed as means ± SE. The comparisons were performed by using one-way analysis of variance when only two means had to be tested. Changes in the measured parameters, occurring before, during, and after exercise, were then analyzed by a two-way analysis of variance, with consideration of the effect of heart transplantation and the effect of exercise. A posteriori Tukey’s test was used after analysis of variance to evaluate when means of controls and HTR were significantly different from baselines and from each other. Relationships between two groups of variables were assessed by calculating the Pearson correlation coefficient. Statistical significance required a P < 0.05.

RESULTS

Baseline period. The clinical and biological characteristics of the two groups are summarized in Table 1, showing that subjects were matched for age and weight and that the mean time elapsed since transplantation was 37.4 ± 7.5 mo. At rest, oxygen uptake, hematocrit, and osmolality were not different in the two groups, but plasma creatinine was greater in HTR.

Hemodynamic and echocardiographic characteristics of the two groups are presented in Table 2. As a result of cardiac denervation, HTR had higher resting heart rate than did controls. Systemic systolic and mean blood pressures tended to be higher and diastolic blood pressure was significantly increased after heart transplantation. The IVST, the LVPWT, and the LVM tended to be increased in HTR, in association with this moderate systemic hypertension. As expected, the left ventricular systolic function was normal in HTR, as inferred from their normal fractional shortening.

Resting plasma ANP and BNP levels were significantly increased in HTR compared with normal subjects (15.2 ± 3.7 vs. 4.4 ± 0.8 pmol/l, P < 0.01, and 14.3 ± 2.6 vs. 7.4 ± 0.6 pmol/l, P < 0.01, for ANP and BNP, respectively). Baseline plasma catecholamines were similar in both groups (1,694 ± 346 vs. 1,578 ± 81 pmol/l for norepinephrine and 143 ± 33 vs. 165 ± 21 pmol/l for epinephrine, in HTR and controls, respectively).

Effect of exercise. Figure 1 shows the characteristics of the exercise in both controls and HTR. As previously reported (18, 20, 33), the maximal tolerated power and the maximal oxygen consumption were lower in HTR than in controls (123 ± 12 vs. 199 ± 14 W, P < 0.001, and 22.8 ± 1.6 vs. 30.3 ± 2.0 ml · min⁻¹ · kg⁻¹, P < 0.01, respectively). The exercise duration was similar in both groups (11.2 ± 0.4 vs. 11.1 ± 0.3 min in HTR and controls, respectively). Exercise-induced plasma volume decrease, inferred from the hematocrit and the hemoglobin increases from rest to peak exercise, was significant but did not differ between groups (−14.7 ± 2.2%, P < 0.001, vs. −9.1 ± 2.3%, P < 0.01, in HTR and controls, respectively).

Table 1. Baseline clinical and biological characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>HTR</th>
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<tr>
<td>Age, yr</td>
<td>42.3 ± 1.7</td>
<td>44.9 ± 2.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.0 ± 4.9</td>
<td>72.0 ± 4.5</td>
</tr>
<tr>
<td>Delay, mo</td>
<td>37.4 ± 7.5</td>
<td>37.4 ± 7.5</td>
</tr>
<tr>
<td>VO₂, ml · min⁻¹ · kg⁻¹</td>
<td>5.0 ± 0.3</td>
<td>5.6 ± 0.4</td>
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<tr>
<td>Hematocrit, %</td>
<td>41.2 ± 1.3</td>
<td>38.4 ± 1.4</td>
</tr>
<tr>
<td>Osmolality, mosmol/kgH₂O</td>
<td>288 ± 2</td>
<td>288 ± 4</td>
</tr>
<tr>
<td>Creatinine, µmol/l</td>
<td>93.8 ± 4.2</td>
<td>123.4 ± 6.6*</td>
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Values are means ± SE. HTR, heart transplant recipients; Delay, mean time elapsed since transplantation; VO₂, oxygen uptake. *Difference compared with control, P < 0.01.
controls, respectively). Osmolality increased similarly in both groups from rest to peak exercise (from 288 ± 4 to 295 ± 4 mosmol/kg H2O, P < 0.001, in HTR and from 288 ± 2 to 297 ± 3 mosmol/kg H2O, P < 0.001, in controls). Similarly, sodium and potassium increased significantly and similarly in both groups (from 136 ± 1.1 to 139 ± 1.8 mmol/l, P < 0.01, in HTR and from 138 ± 0.4 to 142 ± 0.5 mmol/l, P < 0.01, in controls for sodium; and from 5.5 ± 0.1 to 6.0 ± 0.2 mmol/l, P < 0.01, in HTR and from 5.3 ± 0.2 to 5.9 ± 0.3 mmol/l, P < 0.01, in controls for potassium).

Exercise-induced oxygen uptake is shown in Fig. 2. Oxygen uptake increased significantly in both groups, but such increase was lower after heart transplantation (from 5.6 ± 0.4 to 22.8 ± 1.6 ml·min⁻¹·kg⁻¹, P < 0.0001, in HTR; and from 5.0 ± 0.3 to 30.3 ± 2.0 ml·min⁻¹·kg⁻¹, P < 0.0001, in controls).

The heart rate response to exercise is displayed in Fig. 3. Heart rate increased significantly during exercise in both groups, but maximal heart rate was lower in HTR (from 100.4 ± 4.2 to 160.0 ± 5.1 beats/min; P < 0.001) than in controls (from 81.5 ± 4.3 to 180.1 ± 9.7 beats/min; P < 0.0001). Of note, if heart rate change was similar in HTR and controls from 75% to peak exercise, the heart rate increase was significantly delayed during early exercise in HTR (31 ± 2 vs. 86 ± 9%, P < 0.001, in HTR and controls, respectively). The time courses of heart rate and oxygen uptake were similar (Figs. 2 and 3) so that significant positive correlations were observed between heart rate and oxygen consumption from rest to 75% workload (r = 0.71, P = 0.03 and r = 0.91, P = 0.0003 in HTR and controls, respectively) and from rest to peak exercise (r = 0.79, P = 0.009 and r = 0.91, P < 0.0001 in HTR and controls, respectively).

Systolic and mean systemic blood pressures increased significantly from rest to peak exercise in both groups (from 148 ± 6 to 214 ± 11 mmHg, P < 0.001, and from 132 ± 6 to 200 ± 10 mmHg, P < 0.001, for systolic blood pressure; and from 113 ± 5 to 130 ± 11 mmHg, P < 0.05, and from 99 ± 5 to 120 ± 8 mmHg, P < 0.01, for mean systemic blood pressure, in HTR and controls, respectively). As previously reported (2, 32), diastolic blood pressures failed to change significantly in both groups (from 96 ± 3 to 90 ± 8 mmHg and from 83 ± 5 to 81 ± 6 mmHg, in HTR and controls, respectively).

The hormonal responses to exercise are presented in Figs. 4 and 5. Figure 4 outlines the significant differences observed for plasma ANP and BNP secretions before, during, and after exercise in controls and in HTR. At all times, plasma ANP and BNP concentrations were significantly higher in HTR than in controls. Exercise induced a significant ANP increase in HTR (from 15.2 ± 3.7 to 32.8 ± 6.0 pmol/l; P < 0.01) and in controls (from 4.4 ± 0.8 to 12.8 ± 3.0 pmol/l; P < 0.05), but the kinetic of ANP change was different between groups. Particularly, plasma ANP concentrations tended to increase earlier in HTR than in controls. Circulating BNP increased significantly only in HTR (from 14.3 ± 2.6 to 19.0 ± 2.4 pmol/l; P < 0.01) and did not change significantly in controls (from 7.4 ± 0.7 to 8.5 ± 0.7 pmol). Maximal ANP level was reached at 10 min of
recovery after transplantation and decreased thereafter until the 30th min of recovery in both groups. Circulating BNP levels remained significantly elevated during recovery in HTR, compared with resting values ($P < 0.05$).

When the relative hormonal changes are considered, maximal ANP changes were not different in both groups (167 ± 34% in HTR vs. 216 ± 47% in controls; $P = $ not significant) but BNP increase was enhanced in HTR (37 ± 8 vs. 16 ± 8%; $P = 0.05$).

A significant and negative correlation was observed in HTR between plasma ANP and heart rate changes, from rest to 75% exercise ($r = -0.76$, $P < 0.05$; Fig. 3, bottom). Furthermore, circulating ANP and BNP were correlated, weakly but significantly, during exercise in HTR ($r = 0.54$, $P = 0.03$). Finally, a significant and positive correlation was observed between BNP increment from rest to peak exercise and LVMI after heart transplantation ($r = 0.83$, $P = 0.02$).

Time course of plasma catecholamines is shown in Fig. 5. Exercise-induced increase in catecholamines was significant in both groups. However, whereas norepinephrine peak value was similar in HTR and controls, epinephrine peak value was lower in HTR ($P < 0.05$). Thus norepinephrine increased from 1,694 ± 346 to 9,402 ± 804 pmol/l ($P < 0.01$) in HTR and from 1,578 ± 81 to 9,368 ± 1,190 pmol/l ($P < 0.01$) in controls. Epinephrine increased from 143 ± 33 to 1,427 ± 277 pmol/l ($P < 0.05$) in controls, from rest to peak exercise. During recovery, plasma catecholamines decreased rapidly, with preexercise values being reached after 10 or 30 min of recovery for epinephrine and norepinephrine, respectively. Significant correlations were observed between catecholamines and heart rate in both groups ($r = 0.73$, $P = 0.005$ in HTR and $r = 0.74$, $P = 0.008$ in controls, for norepinephrine; and $r = 0.46$, $P = 0.06$ in HTR and $r = 0.70$, $P = 0.009$ in controls, for epinephrine).

DISCUSSION

The major finding of this study is to demonstrate an enhanced exercise-induced BNP increase after heart transplantation, together with a similar ANP response in HTR and controls. Furthermore, BNP increment was positively correlated with LVMI, and an inverse relationship between ANP and heart rate change was observed from rest to 75% maximal exercise in HTR.
Increased circulating ANP and BNP after heart transplantation. ANP and BNP increase in HTR appears to result likely from latent cardiac and/or vascular dysfunction, associated with pressure and/or volume overloads (1, 2, 11, 12, 16, 33). Besides the direct stimulation of the gene encoding for ANP by corticoids, cyclosporine and prednisolone may act by increasing the cardiac pre- and afterload through their vasoconstrictive, nephrotoxic, and fluid retention properties. These medications could therefore have a profound effect on the peptides’ release and clearance, participating thus in ANP and BNP elevation. During exercise, although we cannot exclude the possibility that the cardiac hormones’ increase might be attributable to their decline in clearance, we will mainly discuss the factors modulating ANP and BNP release because their increased concentration appears to be due more to an increased release than to a decreased clearance rate.

ANP response to maximal exercise after heart transplantation. Exercise-induced ANP increase appears to result mainly from increased atrial stretch and/or wall stress in normal humans (9, 25). In HTR, altered atrial anatomy has been first proposed to be responsible for ANP hypersecretion during exercise because, according to the Laplace’s law of the heart, an increased atrial volume results in increased atrial contractile function (19, 40). Furthermore, an increased atrial mass may augment the heart’s ability to release ANP. However, maximal atrial ejection force is similar in HTR and controls, and ANP hypersecretion is also observed in HTR with total excision of the recipient atria (11, 17).

Although catecholamines may stimulate the ANP secretion during exercise in HTR (3, 35), no relationship was found between both parameters. Thus, if peak norepinephrine was similar in both groups, the maximal epinephrine level was lower in HTR than in controls (33, 34). The lower peak power output observed in HTR, together with the suppression of endogenous glucocorticoid, could explain such result (33, 34).

As in controls, rather than ventricular stretch (21), atrial stretch may be the most likely explanation for the ANP increase during exercise after heart transplantation. It has been therefore proposed that, as observed in subjects taking beta-blockers (24), ANP hypersecretion in HTR may reflect a greater atrial stretching, resulting from heart rate and venous return mismatch, secondary to the cardiac denervation-induced chronotropic limitation (33). Indeed, the increase in cardiac output necessary to increase oxygen delivery can be met by an increase in stroke volume and/or heart rate. In HTR, who present with a delayed heart rate increase, the workload demand must be met by an increase in stroke volume and thus a greater distension of the atria due to the increase in preload. Accordingly, the smaller than normal heart rate increase and the ANP elevation were

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negatively correlated in HTR from rest to 75% peak exercise. Moreover, this relationship did not continue through maximal exercise because then circulating catecholamines stimulate directly the sinus node, allowing an increase in cardiac output through heart rate increase at a relative expense of preload.

In accordance with previous studies (36, 37), we nevertheless observed a similar exercise-induced ANP increase in controls and HTR. This may be due to the lower than normal maximal power reached after transplantation, which limits the exercise-induced intracardiac pressures rise, reducing thus ANP increase (4). Additionally, the delayed heart rate response observed in our patients, studied late after transplantation, may not have been sufficient enough to result in exaggerated ANP release during exercise. Indeed, an attenuated ANP increase has been observed in HTR, who showed a nearly normal heart rate response to exercise (13).

BNP response to maximal exercise after heart transplantation. BNP is thought to be released mainly from the ventricles in a constitutive manner, and it has been proposed that short exercise duration could be unable to stimulate synthesis and/or secretion of the cardiac hormone. Accordingly, we and all but one report (28) showed a lack of significant BNP change in response to exercise in normal subjects (26, 29, 30). However, in agreement with previous data on patients with congestive heart failure, ischemia, and/or hypertension (23, 26–30, 38), exercise induced a significant BNP increase in HTR.

Both ANP and BNP have been observed in granules located in cardiac atria, suggesting that BNP may be cosecreted with ANP from the atrium (14, 22). Thus we observed a positive correlation between circulating BNP and ANP during exercise in HTR. Nevertheless, BNP release is not necessarily proportional to ANP, indicating that BNP may originate not only from the atrial granules but also from other tissues such as the ventricles (39). Accordingly, the correlation coefficient between both cardiac hormones is low, further suggesting that atrial cosecretion may not totally explain the enhanced BNP response observed in HTR (39).

Resting plasma BNP levels progressively rise with increasing severity of hypertension. Similarly, the exercise-induced increase in BNP is greater in hypertensive patients with left ventricular hypertrophy, a positive correlation being observed between BNP increment and the LVMI (23, 30). Accordingly, BNP increment from rest to peak exercise and LVMI positively correlated after heart transplantation. Although not demonstrating a causal relationship, because a considerable amount of BNP is secreted from the hypertrophied ventricle, these data suggest that the exaggerated BNP increase of HTR during exercise is also related to LVMI, directly and/or through cardiac diastolic dysfunction.

Indeed, it has been very recently reported that the relationship between LVMI and BNP may be partly explained by diastolic dysfunction. Thus Cheung (5) demonstrated a negative correlation between plasma BNP level and the mitral E/A ratio (peak mitral E wave/peak mitral A wave), recognized index of diastolic function, in patients showing a LVMI similar to that of our HTR. Although the E/A ratio cannot be used in HTR because both atria are electrically isolated and contract independently (11), cardiac diastolic dysfunction might participate in the exaggerated BNP response to exercise after heart transplantation. Indeed, both altered late-diastolic passive left ventricular properties and blunted acceleration of left ventricular relaxation during exercise contribute to the exaggerated exercise-induced elevation of left ventricular end-diastolic pressure in HTR (18, 31). Accordingly, enhanced BNP is correlated to left ventricular end-diastolic pressure at rest and throughout exercise in cardiovascular patients (27, 28), and, even if left ventricular hypertrophy is lacking, alterations in diastolic function are observed in animals and patients with hypertension (4, 15).

In conclusion, despite the fact that exercise-induced ANP release was similar in controls and HTR, sinus node denervation might have a stimulatory effect on ANP secretion after heart transplantation. Moreover, we reported for the first time an exaggerated exercise-induced BNP release after transplantation, related to the LVMI of HTR. Further invasive studies will be useful to investigate specifically the role of cardiac diastolic dysfunction in relation to increased LVMI and whether such enhanced BNP increase might ameliorate the lusitropic response of the transplanted heart during exercise.

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BRAIN NATRIURETIC PEPTIDE RESPONSE TO EXERCISE


