Mechanisms involved in increased plasma brain natriuretic peptide after heart transplantation

Samy Talha*, Anne Charloux, Irina Enache, François Piquard, and Bernard Geny

Department of Physiology and Functional Explorations, Hôpitaux Universitaires de Strasbourg, and Equipe d’Accueil 3072, Université de Strasbourg, 1 Place de l’Hôpital-BP 426, 67091 Strasbourg Cedex, France

Received 26 April 2010; revised 30 September 2010; accepted 13 October 2010; online publish-ahead-of-print 20 October 2010

Abstract

Increased brain natriuretic peptide (BNP), reflecting increased ventricular wall stress and pressure, is a well-known diagnostic and prognostic marker in patients with chronic heart failure. Heart transplantation (HT), the process of replacing the failing heart and restoring haemodynamics, should normalize cardiac endocrine function. Nevertheless, BNP levels remain raised after HT, likely because of increased secretion and/or decreased clearance of the cardiac hormone. Thus, BNP increases in proportion to the extent of left and right ventricular dysfunction after HT. Clinically complicated cardiac transplantation (cardiac systolic dysfunction, renal failure) is associated with the higher level of circulating BNP, and clinically successful cardiac transplantation (mild cardiac diastolic dysfunction) is associated with moderately increased BNP values. Surprisingly, however, increased BNP has also been found after HT in the absence of haemodynamic perturbations or allograft rejection, raising the hypothesis that even subtle modification in the immune system might influence BNP expression. In view of the potential interest in the cardiac hormone for subjects’ risk stratification and therapy, a better knowledge of the mechanisms involved in the BNP increase after HT might be helpful for HT recipients’ follow-up.

Keywords

Natriuretic peptides • Transplantation • Haemodynamics • Inflammation

1. Introduction

Brain natriuretic peptide (BNP), a hormone predominantly secreted by the heart, is a 32-amino-acid polypeptide forming a 17-amino-acid ring with a disulfide bridge between two cysteine residues. BNP is known to have, through intracellular cGMP activation, natriuretic, diuretic, vasorelaxant, antifibrotic, and positive lusitropic properties as well as an inhibiting action on the renin–angiotensin–aldosterone system. As a result, BNP participates in normal fluid homeostasis and blood pressure regulation.

Typically, BNP is highly secreted by the heart in response to myocardial stretch induced by pressure and volume load related to cardiac dysfunction, regardless of its origin. Consequently, natriuretic peptides increase during heart failure (HF), although their plasmatic levels are inadequate to maintain clinical compensation. Therefore, BNP is considered as a useful haemodynamic marker to establish the diagnosis and prognosis of patients with chronic HF.

Heart transplantation (HT), the process of replacing the failing heart and restoring haemodynamics, should, in effect, normalize the neuroendocrine balance. However, many studies have shown that BNP plasma levels remain generally elevated in HT recipients (Htx), when compared with controls. As expected, relationships are also observed between increased BNP and left ventricular (LV) diastolic dysfunction, even in cases of normal LV ejection fraction.

In non-transplanted subjects, increased plasma BNP levels have been shown to be related to right ventricular (RV) functional impairment. According to several authors, such significant relationships between high plasma BNP levels after HT and right atrial, RV, and/or systolic or mean pulmonary artery pressures have been reported by several authors.

Importantly, increased BNP has also been observed in Htx patients without signs of cardiac alterations. This suggests that the cardiac hormone should not be considered exclusively as a haemodynamic marker.

In view of the potential beneficial effects of BNP (prognostic value, cardio-renal, and cellular protections) after HT, we sought to better understand the underlying and controversial mechanisms leading to elevated BNP in Htx patients.

2. Levels of BNP after HT

HT replaces the failing heart and usually restores the patient’s cardiac and haemodynamic status. Therefore, normalization of the neuroendocrine biomarkers is expected.

* Corresponding author. Tel: +33 369 55 13 68; fax: +33 369 55 18 83, Email: samy.talha@chru-strasbourg.fr
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oup.com.
Accordingly, the renin–angiotensin–aldosterone system is normalized after cardiac transplantation (after a transient increase due to surgical stress), although plasma cardiac hormone levels remain high. After an initial decrease related to cardiovascular and respiratory improvement of the patients, plasma BNP levels rise as early as the first post-operative days. This is not due to the cardiac surgery setting because BNP values have been shown to remain within normal ranges in coronary–artery bypass patients. Thereafter, consistent data demonstrated a progressive time-dependent decline in plasma BNP concentration in adult Htx patients, although hormonal levels remained elevated.

In healthy children, plasma BNP levels significantly decrease from infancy to adolescence, and then subsequently increase at the onset of puberty to finally reach adult levels. The interpretation of BNP kinetics in children after HT thus appears to be more difficult and discrepancies may be related to the age of the transplanted patients.

Increased circulating BNP after HT may be explained by a reduced degradation and/or an enhanced secretion of the cardiac hormone (Figure 1). Indeed, two factors can increase or decrease hormone blood levels. One is the velocity of hormonal release in the blood and the second is the proportion of circulating hormone decreasing per unit time, also called metabolic clearance. The plasma is cleared of hormones through various mechanisms, including renal excretion, enzymatic degradation, or endocytosis of hormone-receptor complex.

In this review, we will first discuss the available data concerning metabolic clearance, and the modulatory effects of surgical and medical therapies on endothelial function, ventriculo-vascular coupling, and plasma BNP levels in Htx patients. The relationship between plasma BNP levels and haemodynamic abnormalities (left and right systolic and diastolic functions) will not be elaborated because it is firmly established. Next, we will discuss the effects of chronic and acute rejection, and finally, we will examine the possibility that increased BNP after HT may not be constantly due to haemodynamic alterations, but may also be related to an inflammatory process without detectable cardiovascular consequences.

3. Potential non-cardiac function-related mechanisms explaining increased circulating BNP after HT

3.1 Reduced degradation: metabolic clearance and renal function

In addition to being removed from blood flow after binding to natriuretic peptide receptor type-C or possibly receptor type-A, BNP can also be cleared by renal excretion or through proteolysis by peptidases, the most studied of which is neutral endopeptidase (NEP; EC 3.4.24.11), a zinc metalloproteinase.

Moreover, an ubiquitous cell-surface protease, aminopeptidase dipeptidyl-peptidase IV (EC 3.4.14.5), also cleaves BNP 1–32 to produce BNP 3–32 with an efficiency higher than or comparable to several known in vivo substrates of the enzyme. This BNP 3–32 has reduced renal actions and lacks vasodilating properties.
our knowledge, very little data are available on pathophysiological specificities of BNP degradation through these pathways in the HT population. One report has demonstrated an enhanced natriuretic response to NEP inhibition in heart-transplant recipients, likely related to ANP but not to an increase in BNP. BNP is also cleared by glomerular filtration, hence explaining a probable influence of renal function on Htx cardiac hormone levels. Conversely, it was also demonstrated that elevated plasma BNP failed to correlate with creatinine levels, even in the presence of increased levels of creatinine. In fact, renal function probably has little influence on circulating BNP values, and 60 mL/min/plasma BNP failed to correlate with creatinine levels, even in the presence of increased levels of creatinine. 10,43 Conversely, it was also demonstrated that elevated plasma BNP failed to correlate with creatinine levels, 10,43 even in the presence of increased levels of creatinine. 9,11 In fact, renal function probably has little influence on circulating BNP values, and 60 mL/min/plasma BNP failed to correlate with creatinine levels, 10,43 even in the presence of increased levels of creatinine. 9,11 In fact, renal function probably has little influence on circulating BNP values, and 60 mL/min/plasma BNP failed to correlate with creatinine levels, 10,43 even in the presence of increased levels of creatinine. 9,11 In fact, renal function probably has little influence on circulating BNP values, and 60 mL/min/plasma BNP failed to correlate with creatinine levels, 10,43 even in the presence of increased levels of creatinine. 9,11

3.2 Enhanced secretion

3.2.1 Surgical and medical treatments

Discrepancies exist regarding the influence of the surgical procedure (i.e. bicaval vs. bi-atrial HT) and cardiac denervation on plasma natriuretic peptide levels after HT. Nevertheless, cardiac denervation likely contributes in increasing BNP secretion through salt-sensitive hypertension and fluid retention in Htx patients; both mechanisms being enhanced by immunosuppressive therapy.

Furthermore, cyclosporine, similar to other calcineurin inhibitors such as tacrolimus, is also thought to induce vasoconstriction and salt retention, and participates in rising systemic blood pressure. However, except in cases of major increases in blood pressure likely associated with cardiac diastolic dysfunction, these disturbances are generally not sufficiently important in patients under low dose maintenance immunosuppressive therapy to increase their plasma BNP levels. Accordingly, these abnormalities in blood pressure and fluid homeostasis have not been observed in liver transplant recipients receiving cyclosporine; hence, the observed increase in BNP, as in the case of Htx patients, cannot be attributed to cyclosporine alone. As for corticosteroids, a successful reduction in prednisone dosage may reflect a reduced ventricular wall stress associated with a reduced BNP level after HT. Nevertheless, some studies failed to show any statistical relationship between plasma BNP levels and steroids or immunosuppressive drugs.

3.2.2 Ventriculo-vascular uncoupling and endothelial function

Ventriculo-vascular uncoupling possibly participates in the increase in BNP observed after HT, because it contributes to LV hypertrophy and diastolic function abnormalities of the allograft. Conversely, replacing the failing heart by a so-called ‘normal’ heart does not completely restore cardiovascular function. Indeed, endothelial dysfunction developed before HT, i.e. during the HF period, may even be enhanced by immunosuppressive therapy following transplantation. There are no studies investigating the direct effect of endothelial dysfunction on resting BNP in Htx patients, but since endothelial dysfunction likely participates in exercise capacity limitation after HT, it may also participate in the exercise-induced increase in BNP in Htx patients. Given its vasodilatory properties, BNP increase during exercise may represent an adaptive response to reduced shear-stress-mediated vasodilatation observed after HT.

3.2.3 Rejection

The prognosis of Htx patients following the orthotopic procedure has greatly improved over the past 20 years. Cardiac allograft vasculopathy (CAV) and/or acute cardiac rejection contribute to the increase in BNP when rejection episodes impair heart function in a significant manner. Moreover, increased BNP has often been related to CAV and acute rejection even when cardiac function is not compromised.

3.2.3.1 Cardiac allograft vasculopathy

Long-term survival of allografted hearts is limited by a progressive fibro-proliferative disease, resulting in intimal thickening and occlusion of the grafted coronary vessels, called CAV. Hence, in previous studies aimed at establishing whether plasma BNP could be a prospective screening tool for CAV, the latter was indeed found to be associated with elevated plasma BNP levels. In addition, a higher BNP level was associated with a lower survival rate. BNP concentration was also shown to predict new episodes of serious CAV, independent of haemodynamic measurements. Interestingly, natriuretic peptides have potent anti-proliferative and anti-migratory effects on vascular smooth muscle cells and have a potential role in the pathogenesis of coronary atherosclerotic plaque. Indeed, Casco et al. have shown the presence of both mRNA and its translation products for all three NPs and their receptors in human coronary atherosclerotic plaque. According to these authors, this coronary NP autocrine/paracrine system may be involved in the regulation of intimal plaque formation in humans and in vascular remodelling during CAV progression.

3.2.3.2 Acute graft rejection

Acute graft rejection is also a major cause of premature or late mortality after HT and represents 30% of global deaths, the great majority (86%) of which occur during the first 3 months after surgery. At the present time, myocardial biopsy is the gold standard for the diagnosis of acute rejection; however, this is an invasive technique and thus has some drawbacks. Studies have, therefore, been performed to assess whether a simple laboratory measurement of plasma BNP could be useful in selecting patients for subsequent biopsy. Results have been conflicting: on the one hand, many studies conducted in adults have failed to observe any relationship between plasma BNP levels and histological grades of rejection; on the other hand, many studies have demonstrated a link between plasma BNP levels and not only the presence and the degree of rejection (rejection grades ≥2, or ≥3, or rejection grades 2 to 4), but also the delay of occurrence of rejection after HT (only within the first 90 days). Other authors have observed a significant relationship between BNP, or BNP combined with Doppler tissue imaging, and rejection. Some have proposed that plasmatic BNP level determination could participate in rejection diagnosis, even in paediatric Htx patients. In contrast, Atonu et al. failed to observe any significant difference in mean plasma BNP concentrations in adolescents presenting with and without a rejection episode.

Finally, from these results, it appears that BNP should only be used as a complementary diagnostic tool for cardiac rejection detection in adults, its value being higher during the first 90 days after HT and when rejection grades are high. A within-individual change in BNP over time appears to be more helpful than absolute BNP in detecting rejection grades ≥2. In children, increased BNP may be more reflective of acute rejection, likely because children have fewer co-morbid conditions inducing high plasma BNP levels.

3.2.4 Immunosuppressive therapy

As for corticosteroids, a successful reduction in prednisone dosage may reflect a reduced ventricular wall stress associated with a reduced BNP level after HT. Nevertheless, some studies failed to show any statistical relationship between plasma BNP levels and steroids or immunosuppressive drugs.
Table 1 Increased plasma BNP and rejection (grades and delay of occurrence) in adult heart-transplanted patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Controls BNP (pg/mL)</th>
<th>Heart transplant recipients</th>
<th></th>
<th>BNP (pg/mL)</th>
<th>Rejection</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age (years)</td>
<td>Graft delay (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Masters et al.19</td>
<td>–</td>
<td>56 ± 3 (n = 10)</td>
<td>4.2 ± 0.8</td>
<td>198 ± 12a</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td>544 ± 116</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td>Hervas et al.12</td>
<td>16.7 ± 16.2 (n = 34)</td>
<td>53 ± 11 (n = 80)</td>
<td>N/A</td>
<td>162 ± 188</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>163 ± 145</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>227 ± 258e</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>380 ± 1455e</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td>Bader et al.27</td>
<td>–</td>
<td>N/A (n = 144)</td>
<td>42 ± 50</td>
<td>≤117</td>
<td>No/mild/severe</td>
<td>48/56/42% (respectively)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;117</td>
<td>No/mild/severe</td>
<td>52/44/58% (respectively)</td>
</tr>
<tr>
<td>Hervas et al.9</td>
<td>17 ± 16 (n = 36)</td>
<td>54 ± 10 (n = 81)</td>
<td>0.5–15</td>
<td>494 ± 462</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>268 ± 245a</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>163 ± 289</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>137 ± 199</td>
<td>&lt;3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>510 ± 470b</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>142 ± 203</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>170 ± 297</td>
<td>≥3A</td>
<td></td>
</tr>
<tr>
<td>Arnau-Vives et al.11</td>
<td>17 ± 16 (n = 36)</td>
<td>53 ± 11 (n = 71)</td>
<td>0–15</td>
<td>278 ± 255</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>510 ± 470b</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>142 ± 203</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>170 ± 297</td>
<td>≥3A</td>
<td></td>
</tr>
</tbody>
</table>

Means ± SD or medians. Number of patients is indicated in parentheses. BNP, plasma concentrations of brain natriuretic peptide. Rejection, when it occurs, is displayed by grade (0–4) or severity (mild or severe). N/A, data not available.

aSignificantly different from grade ≥2.
bSignificantly different from no rejection.
cSignificantly different from grades 0 and 1.
dSignificantly different from 42 ± 50.

---

Table 2 Increased plasma BNP despite normal right and left heart functions in heart-transplanted patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (years)</th>
<th>Graft delay (months)</th>
<th>BNP (pg/mL)</th>
<th>Right heart</th>
<th>Left heart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RAP (mmHg)</td>
<td>sPAP (mmHg)</td>
</tr>
<tr>
<td>Ationu et al.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctrl</td>
<td>N/A (n = 20)</td>
<td>15 ± 2 (n = 14)</td>
<td>20 ± 1.8</td>
<td>202 ± 16a</td>
<td>5.8 ± 0.7</td>
</tr>
<tr>
<td>Htx</td>
<td></td>
<td>11.8 ± 3.3 (n = 13)</td>
<td>0.1–6.8</td>
<td>82 ± 12a</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Kirchhoff et al.31</td>
<td></td>
<td>49 (n = 14)</td>
<td>0–1</td>
<td>188 ± 181.5</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7–12</td>
<td>77 ± 57b</td>
<td>6.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Mehra et al.43</td>
<td></td>
<td>58 ± 10 (n = 28)</td>
<td>4 ± 0.8</td>
<td>255 ± 32</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>De Sylos et al.79</td>
<td></td>
<td>11 (n = 33)</td>
<td>6–163</td>
<td>65.8 (no R)</td>
<td>7.0 ± 2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>144.2c (R)</td>
<td>6.0 ± 1.3</td>
<td>22.0 ± 6.2</td>
</tr>
<tr>
<td>Talha et al.49</td>
<td></td>
<td>45.1 ± 2.7 (n = 12)</td>
<td>4.0 ± 0.9</td>
<td>N/A</td>
<td>19.8 ± 1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.0 ± 4.2 (n = 12)</td>
<td>97.8 ± 14.2</td>
<td>33.8 ± 8.5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values are means ± SD or medians or range. Number of patients is indicated in parentheses. N/A, data not available; BNP, plasma concentrations of brain natriuretic peptide; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; sRVP, systolic right ventricular pressure; dRVP, diastolic right ventricular pressure; PCWP, pulmonary capillary wedge pressure; EF, ejection fraction; Ctrl, controls subjects; Htx, heart transplant patients; R, rejection.

aSignificant difference with controls.
bSignificant difference with 1 month.
cSignificant difference with no rejection.
4. Why does BNP remain elevated after HT despite a ‘normal’ cardiovascular function? The inflammatory hypothesis

Very interestingly, recent studies support the view that factors other than haemodynamics may be involved in the activation of the cardiac natriuretic peptide system after HT. In the past, the potential role of non-haemodynamic factors participating in the increase in BNP was probably occulted by the presence of LV diastolic dysfunction. Major advances in organ preservation, surgical procedures, immunosuppression as well as other medical therapeutics, including a larger use of angiotensin-converting enzyme inhibitors, angiotensin type-1 receptor blockers and statins, all known for their beneficial effects on cardiac remodelling, cardiac allograft rejection, and survival, may partially explain these new discoveries.75–78

Some studies have failed to observe any correlation between high BNP plasmatic levels and cardiac functions (Table 2). In 28 clinically quiescent HT patients, without dyspnoea and with normal LVEF and haemodynamics (right atrial pressure, PCWP, and cardiac index), Mehra et al.43 observed an elevated BNP concentration. Masters et al.69 did not report any significant linear correlation between PCWP, right atrial pressure, and BNP plasma in a small subset of patients. Similarly, in 14 heart transplant recipients, Ationu et al.30,34 did not observe any relationship between high levels of RV tissular and plasmatic BNP, and right intracardiac pressures. Moreover, Kirchhoff et al. noted a normalization of LV and RV haemodynamics (systolic and diastolic) without a parallel normalization of BNP in the year following HT, suggesting the potential role of factors other than haemodynamics.31,43 Finally, using echocardiography, we recently selected 12 Htx patients with normal left and right heart systolic and diastolic functions from a cohort of 26 well-being recipients, and compared their circulating BNP values with those of 12 age-, body mass index-, LV mass index-, and mean arterial pressure-matched controls. Despite their normal cardiac functions, these Htx patients presented with significantly increased BNP values, when compared with controls (Figure 2).49

Altogether, these data have given evidence to the concept that circulating BNP may be increased after HT even when cardiovascular functions are regarded as normal using commonly used methods. On a cellular level, one may hypothesize that increased circulating BNP in Htx patients may reflect an increased secretion by cardiomyocytes or other cell types infiltrating the heart in response to immunological and/or inflammatory stimulations. Studies showing increased BNP during rejection, despite normal haemodynamics, argue in favour of this hypothesis.79

4.1 BNP remains increased in Htx patients with normal left and right cardiac functions

Some studies have failed to observe any correlation between high BNP plasmatic levels and cardiac functions (Table 2). In 28 clinically quiescent HT patients, without dyspnoea and with normal LVEF and haemodynamics (right atrial pressure, PCWP, and cardiac index), Mehra et al.43 observed an elevated BNP concentration. Masters et al.69 did not report any significant linear correlation between PCWP, right atrial pressure, and BNP plasma in a small subset of patients. Similarly, in 14 heart transplant recipients, Ationu et al.30,34 did not observe any relationship between high levels of RV tissular and plasmatic BNP, and right intracardiac pressures. Moreover, Kirchhoff et al. noted a normalization of LV and RV haemodynamics (systolic and diastolic) without a parallel normalization of BNP in the year following HT, suggesting the potential role of factors other than haemodynamics.31,43 Finally, using echocardiography, we recently selected 12 Htx patients with normal left and right heart systolic and diastolic functions from a cohort of 26 well-being recipients, and compared their circulating BNP values with those of 12 age-, body mass index-, LV mass index-, and mean arterial pressure-matched controls. Despite their normal cardiac functions, these Htx patients presented with significantly increased BNP values, when compared with controls (Figure 2).49

Altogether, these data have given evidence to the concept that circulating BNP may be increased after HT even when cardiovascular functions are regarded as normal using commonly used methods. On a cellular level, one may hypothesize that increased circulating BNP in Htx patients may reflect an increased secretion by cardiomyocytes or other cell types infiltrating the heart in response to immunological and/or inflammatory stimulations. Studies showing increased BNP during rejection, despite normal haemodynamics, argue in favour of this hypothesis.79
4.2 Inflammatory and immune mediators stimulate BNP release by different cell types

4.2.1 Non-specific inflammation

A relationship between elevated NP levels and inflammation has been described in cardiovascular and chronic inflammatory diseases. Indeed, in the Heart Outcomes Prevention Evaluation study of patients with coronary artery disease and without HF, concentrations of NT-proBNP were correlated with elevated levels of soluble tumour necrosis factor (TNF) receptors. In HF, it has been recognized that patients with cardiac cachexia have the strongest immune activation and exhibit the highest TNF-α concentrations. Vaz Pérez et al. showed that these patients display very high plasma levels of ANP and BNP, correlating with TNF-α independent of LV end-diastolic diameter, New York Heart Association functional class, creatinine clearance, and age. The authors suggested that the cardiodepressive and cardiotoxic effects of TNF-α on the myocardium could independently stimulate the production and secretion of NP. Interestingly, soluble TNF receptors were also found to be increased in relation to the severity of HF, and positively correlated with BNP and ANP levels, mean PCWP, and mean pulmonary arterial pressure. Moreover, NT-proBNP concentrations have been found to be increased in patients with rheumatoid arthritis without clinical HF and associated with inflammation and disease activity, as well as linearly associated with C-reactive protein levels.

4.2.2 Immunological insult of the graft after cardiac transplantation

Cytokines play central roles in graft rejection. They increase the expression of adhesion molecules such as interferon (IFN)-γ, interleukin (IL)-1β, and TNF-α are also involved in the activation of CD4+ and CD8+ T-lymphocytes (IL-2 and IFN-γ), B-lymphocytes (IL-2 and IL-4), and in the up-regulation of MHC I and II antigens (IFN-γ and TNF-α). In severe cardiac HF, BNP is not only produced by cardiomyocytes, but also by infiltrating macrophages, endothelial cells, and T-cells. In rat cardiomyocyte cultures, IL-1β was described as a potential transcriptional activator of the promoter element of the BNP gene. Concomitantly, Tsuruda et al. showed in adult canine cultured cardiac fibroblasts that TNF-α also induced BNP secretion.

With regard to HT, increased plasmatic BNP levels during acute cardiac allograft rejection may partly be explained by the ability of pro-inflammatory cytokines (i.e. IL-1β and TNF-α) to selectively increase BNP promoter activity, to modulate cardiomyocyte BNP gene expression, and to enhance BNP secretion through a pathway using p38 mitogen-activated protein kinase signaling. Lipopolysaccharide (LPS), a mediator of inflammation, also directly stimulates BNP gene expression in rats, by specifically targeting the enhancer GATA located in the proximal portion of the BNP promoter. In humans, other cytokines such as RANTES (Regulated one activation, normal T expressed and secreted), NAP-2 (neutrophil-activating protein-2), and IGFBP-1 (insulin growth factor binding protein-1), present in biopsies of cardiac transplants in rejection, have been correlated with circulating plasma BNP levels in these patients.

In cultured neonatal rat ventricular cardiocytes, these cytokines also induce a selective secretion of BNP, but not of ANP. In this respect, it is noteworthy to observe that plasma BNP, in contrast to plasma ANP, can increase specifically in patients with acute allograft rejection. Furthermore, the intensification of immunosuppressor treatment by OKT3, a T-cell monoclonal antibody anti-CD3, has...
shown an effective rejection regression related to a decrease in plasmatic BNP. This BNP regression was not related to a haemodynamic improvement, because plasmatic ANP did not vary specifically in this situation of rejection.\textsuperscript{69} The increase in BNP during an acute rejection episode would then be mediated through T-cell cytokine secretion. This inflammatory process, also observed in an experimental model of autoimmune myocarditis, appears to be related to a specific regulation of BNP, disorganized from that of ANP.\textsuperscript{97} These observations clearly emphasize that the regulation of BNP may distinct from any haemodynamic variations.

Increased cytokine levels have also been observed in quiescent heart, without diagnosed rejection. Torre-Amione et al.\textsuperscript{98} showed that TNF-α is chronically overexpressed in human cardiac allografts in the absence of any histopathological or clinical evidence of rejection and in the presence of normal LV systolic function. Thus, the significant relationship found between elevated BNP concentration and cytokines, alloimmunization, and inflammation genes may partly explain why BNP levels do not systematically correlate with haemodynamic parameters.\textsuperscript{31} Accordingly, upon gene microarray analysis in peripheral blood mononuclear cells of 28 clinically and haemodynamically stable Htx patients, Mehra et al.\textsuperscript{45} observed, in normal haemodynamic situation and in the absence of histological allograft rejection, that BNP elevation is indicative of an upregulation of pathways involved in thrombosis, inflammation, alloimmunization activation, cardiac remodeling, and vascular perturbation. Moreover, HT BNP appears, in turn, to play a protective immunoregulatory role, because it was shown to reduce the total number of monocytes, B cells, and NK cells as well as impair NK cell cytotoxicity and adhesion of non-classical monocytes in an in vitro study using whole blood from 40 stable Htx patients.\textsuperscript{99}

Consequently, BNP elevation not only appears to be a haemodynamic marker, but should also be considered as a factor reflecting the balance between active cardiac injury and repair (Figure 4).\textsuperscript{43}

5. Conclusion

In summary, numerous factors participate in the persistent increase in BNP observed after HT. BNP is known to increase in proportion to the extent of LV and RV dysfunctions after HT. Surprisingly, however, increased BNP has also been found after HT in patients without haemodynamic perturbations or allograft rejection, raising the hypothesis that even subtle modifications in the immune system may influence BNP expression.

Cardiomyocytes and/or other cell types infiltrating the heart may increase their BNP secretion in response to immunological and/or inflammatory stimulations. Elevated BNP may therefore reflect the balance between active cardiac injury and repair at the cellular level. Further studies are required to better understand the mechanisms modulating BNP secretion in order to optimize risk stratification and therapy after HT.

Acknowledgements

The authors thank Mrs A.-M. Leonardo and A. Schmitt for their expert secretarial assistance. We are indebted to Mr Pothier, Mrs J. Kronberg and Mr Y. Kronberg for careful language reviewing of the manuscript.

Conflict of interest: none declared.

References


Brain natriuretic peptide in heart transplantation


87. Ma KK, Ogawa T, De Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004;36:505–513.


