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ORIGINAL ARTICLE

Determinants of B-type natriuretic peptide plasma levels in the chronic phase after heart transplantation*

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Summary

Determinants of B-type natriuretic peptide (BNP) plasma levels in the chronic phase after heart transplantation remain unclear. BNP was measured in 105 stable long-term heart transplant recipients with normal left ventricular function by echocardiography and correlated with clinical, demographic and hemodynamic parameters. Multivariate analysis revealed a significant correlation of BNP with female recipient gender ($P = 0.006$), time post-transplant ($P = 0.006$), donor age ($P = 0.007$), angiographic signs of transplant vasculopathy (TVP) ($P = 0.03$), serum creatinine level ($P = 0.04$), and a strong trend for diastolic dysfunction ($P = 0.09$). Donor gender, recipient age, cyclosporin A blood levels, rejection history, and pulmonary artery pressure had no independent effect on BNP. BNP after heart transplantation appears to be influenced both by established general determinants (female gender, renal function) and transplant-specific determinants such as time post-transplant, donor age and potentially also TVP. In order to determine the value of BNP as a potential surrogate marker of TVP serial intraindividual measurements appear appropriate.

Introduction

B-type natriuretic peptide (BNP) constitutes a valuable neurohormonal marker for diagnosis of left ventricular dysfunction [1–3], risk assessment [4–6], therapeutic monitoring [7,8], and therapy [9] in heart failure (CHF) patients. The approved BNP cut-off for the diagnosis of heart failure in patients with normal renal function is 100 pg/ml (normal range: 5–100) [10]. Elevated BNP indicates left ventricular dysfunction – both systolic and diastolic [1–3]. In the heart transplant setting, however, a distinct role for BNP has not yet been defined. Although a correlation of BNP plasma levels with time post-transplant and hemodynamic parameters early after heart transplantation have been described [11–13], there are currently no data on the influence of demographic and clinical parameters on BNP plasma levels in the chronic phase after cardiac transplantation, including age (recipient or donor), gender or renal function, i.e. parameters known to influence BNP plasma levels in nontransplant patients [2,14,15]. BNP is a marker of ventricular wall stress and appears to reflect hemodynamic alterations and clinical symptoms characteristic of diastolic dysfunction after heart transplantation [12,13]. Myocardial hypertrophy and fibrosis developing early after heart transplantation [16] appear to cause a rise in BNP plasma levels upon exercise in heart transplant recipients [17]. On the contrary, several factors are implicated in the pathogenesis of myocardial hypertrophy and fibrosis after heart transplantation including hypertension [18] and the development of transplant vasculopathy (TVP) [19] suggesting a potential association of BNP with these factors. Furthermore, inflammation appears to contribute to elevated levels of BNP as recently shown by serial intraindividual

measurements for acute allograft rejection in a small group of 10 heart transplant recipients [20].

The present study evaluates demographic, clinical and hemodynamic determinants of BNP plasma levels in heart transplant recipients in the chronic post-transplant phase, aiming to identify potential associations of BNP physiology with transplant-specific factors [rejection, cyclosporin A level, cytomegalovirus (CMV) infection, TVP] and to gain new insights into BNP regulation on the basis of the unique transplant situation characterized by gender mismatch and dissociation of graft and recipient age.

Patients and methods

Study population

The BNP plasma levels were measured at varying times after orthotopic heart transplantation in a total of 105 clinically stable heart transplant recipients with normal left ventricular function (LVEF) by echocardiography presenting to our institution between November 2001 and November 2002 for routine follow up. Complete demographic, clinical, and hemodynamic parameters were available of all heart transplant recipients included in the study. Informed consent was obtained from all patients along with approval from our institutional ethics committee to conduct statistical analysis with patient-related data collected in our single-institution database (MS ACCESS, Microsoft, Seattle, WA, USA).

Exclusion criteria

Heart transplant recipients in the early post-transplant phase (<0.75 years), clinical diagnosis of graft failure, poor LVEF (<40%) or deteriorating LV function (>25% change in 6 months), severe rejection with hemodynamic compromise, acute viral/bacterial infection and/or sepsis, terminal renal failure (serum creatinine >4 mg/dl) or hemodialysis were excluded from this study.

Vital signs and chemistry

Patient arterial blood pressure was obtained using the mean of patient self-measurements over the preceding 4–6 weeks. Laboratory analyses were performed at the time of visit to obtain serum creatinine level, hemoglobin level, cyclosporin A whole blood trough level, CMV serology (and CMV-DNA/antigen if clinically indicated).

Echocardiography

A transthoracic echocardiogram was performed within 8 weeks of BNP measurements to assess left/right ventricular morphology, wall thickness and function with special attention to left/right ventricular diastolic function employing Doppler echocardiography (early and late diastolic flow velocity across the mitral/tricuspid valve into the left/right atrium (V_E, V_A, deceleration time). Diastolic dysfunction was diagnosed upon echocardiographic finding of a decreased deceleration time (DTE < 150 ms) and an increased V_E/V_A ratio (>2).

Endomyocardial biopsy

Routine endomyocardial biopsies were performed in these long-term heart transplant recipients (≥0.75 years post-transplant) in the second and third post-transplant year between 1 and 3 times annually, thereafter biopsies were performed on a yearly basis. Cardiologists and cardiology fellows performed all biopsies, experienced cardiac pathologists reviewed and graded the biopsy specimens according to ISHLT criteria [21]. A rejection index was calculated as follows: ISHLT rejection grades were assigned a point score (ISHLT 0/1A = 0 points, 1B = 1 point, 2 = 2 points, 3A = 3 points, 3B = 4 points, 4 = 5 points). The total point score of all biopsy results of a patient was normalized to the number of biopsies performed to yield the rejection index.

Coronary angiography

All patients underwent routine annual coronary angiography. The results of a coronary angiogram and right heart catheterization performed within 1 year (mean ± SD: 0.6 ± 0.88 years) of BNP measurement were available for the diagnosis of TVP and for the determination of hemodynamic parameters such as pulmonary artery pressure and pulmonary vascular resistance. LV function had to be normal by angiogram, otherwise the patient was excluded from this study. The diagnosis of TVP was determined by coronary angiography. For the purpose of this study, any clear angiographic sign of vessel alteration based on the scoring system developed by Gao *et al.* [22] resulted in the diagnosis of TVP, i.e. focal lesions of more than 25% stenosis (not present on baseline angiogram), diffuse distal narrowing and obliteration or abrupt distal vessel termination. Coronary angiograms were read by two independent reviewers blinded to the results of BNP measurement.

Measurement of BNP plasma levels

For each measurement, 5 ml of whole blood were collected into tubes containing potassium ethylenediaminetetraacetic acid (EDTA; 1 mg/ml blood). BNP was measured using the Triage BNP test (Biosite Diagnostics Inc., San Diego, CA, USA) within 4 h after venipuncture at room

temperature. The triage BNP test is a sensitive and precise fluorescence immunoassay for the quantitative determination of BNP in EDTA whole blood and EDTA plasma specimens, recently approved by the Food and Drug Administration (FDA). The turn around time for one sample is 15 min for this assay and the test result is calculated automatically [23]. BNP plasma levels >100 pg/ml were considered elevated according to the manufacturers' package insert with 97.4% of normal individuals (no congestive heart failure) aged 55–64 (males and females) having lower levels [14].

Statistics

Continous data are presented as the mean value (±SD) for variables with normal distribution. Comparisons between group mean values were made using *t*-test, nonparametric Mann–Whitney *U*-test, chi-square testing or univariate regression analysis as appropriate. To determine independent factors influencing BNP levels in heart transplant recipients multivariate logistic regression analysis was performed (StatView®, SAS Institute Inc., Cary, NC, USA). More than 95% of demographic, clinical and serologic data were available from all patients, therefore multiple regression analysis was performed using all data sets, replacing missing values by group mean. A *P*-value <0.05 was considered statistically significant.

Results

The BNP plasma levels were measured in 105 individual heart transplant recipients presenting to our institution from November 2001 through November 2002 (see Exclusion Criteria in Patients and Methods). This patient population represented a group of long-term survivors as reflected by a mean (SD) follow up of 6.1 (3.7) years (range: 0.75–13.5). As expected in the chronic post-transplant phase renal function was impaired (mean serum creatinine level = 1.57 mg/dl) despite reduced levels of cyclosporin A (138.1 μg/l) compared with target levels of 175–200 μg/l in patients during the first post-transplant year. The immunosuppressive regimen was predominantly based on cyclosporin A (88% of all patients) and only 13 patients (12%) received tacrolimus (FK506). Mycophenolate mofetil was given to long-term heart transplant recipients with deteriorating renal function (50% of patients) replacing azathioprine in order to allow for safe reduction in calcineurin inhibitor dosage for nephroprotection. Statins (84% of all patients) and angiotensin-converting enzyme (ACE) inhibitors (78% of all patients) were routinely administered.

The overall mean BNP plasma level in the group of 105 patients was 179.8 ± 195.3 pg/ml (median 96.8 pg/ml, range: 5–963) (Fig. 1). Patients were divided into two groups using the median BNP level as a cut-off, for the purpose of this pilot study no further subdivision was made. Patient characteristics are shown in Table 1. The patient group with BNP levels above the median was characterized by a higher number of females ($P = 0.04$), a later stage post-transplant ($P = 0.002$), worse renal function ($P = 0.006$) and a higher prevalence of anemia ($P = 0.02$). Furthermore, shorter ischemic pretransplant time ($P = 0.02$), higher prevalence of diastolic dysfunction ($P = 0.02$), higher rejection index ($P = 0.045$), and higher prevalence of TVP ($P = 0.003$) was found in the group with greater BNP levels. The immunosuppressive regimen did not differ significantly in both groups. Thus, the number of patients receiving a cyclosporin A-based immunosuppressive regimen was not significantly different in either group: ±azathioprine ± steroids – group 1: 19 of 52 vs. group 2: 27 of 53 ($P = 0.5$), ±mycophenolate mofetil ± steroids – group 1: 28 of 52 vs. group 2: 18 of 53 ($P = 0.3$). The number of patients receiving a tacrolimus-based regimen did not differ significantly, either: ±azathioprine ± steroids – group 1: four of 52 vs. group 2: three of 53 ($P = 0.98$), ±mycophenolate mofetil ± steroids – group 1: one of 52 vs. group 2: five of 53 ($P = 0.2$). Similar number of patients received ACE-inhibitors – group 1: 40 of 52 vs. group 2: 42 of 53 ($P = 0.96$), and statins – group 1: 44 of 52 vs. group 2: 44 of 53 ($P = 0.9$). No significant differences were found comparing the number of patients receiving aspirin (ASA) – group 1: 12 of 52 vs. group 2: 22 of 53 ($P = 0.2$) and calcium-antagonists – group 1: 34 of 52 vs. group 2: 24 of 53 ($P = 0.3$).

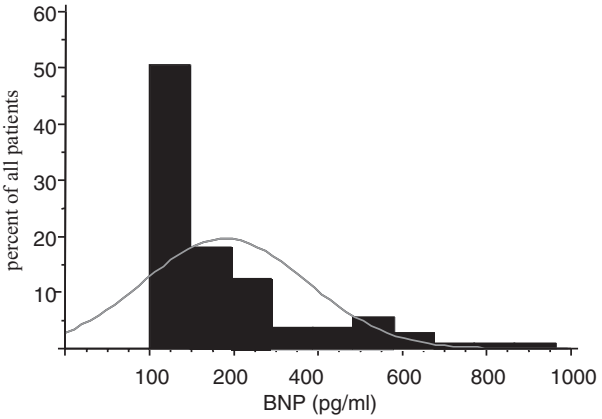

Figure 1 Distribution of B-type natriuretic peptide (BNP) plasma levels in the chronic phase after heart transplantation. The distribution of BNP plasma levels in the 105 long-term heart transplant recipients is shown ranging from 5 to 963 pg/ml. The median of 96.8 pg/ml comprises the first bar reflecting 50% of all patients having BNP plasma levels smaller or equal to 100 pg/ml (shown as percentage of all patients). The peak of the Gauss distribution curve reflects the mean of 179.8 pg/ml.

Table 1. Patient characteristics.

Parameter	Group 1 ($n = 52$): BNP < 96.8 pg/ml	Group 2 ($n = 53$): BNP ≥ 96.8 pg/ml	*P*-value
Recipient age (years)	57.1 ± 11.0	58.3 ± 9.9	NS
Time post-transplant (years)	5.0 ± 3.6	7.2 ± 3.5	0.002
Etiology (ICMP)	17/52 (33%)	18/53 (34%)	NS
Female recipient gender	5/52 (10%)	17/53 (32%)	0.04
Female donor gender	18/52 (35%)	25/53 (47%)	NS
Gender mismatch	19/52 (37%)	16/53 (30%)	NS
Donor age	31 ± 11	38 ± 12	NS
Time of ischemia	185 ± 45.9	162 ± 50.7	0.02
Cyclosporin A level (μg/l)	137.7 ± 61.5	138.5 ± 52.5	NS
Creatinine	1.4 ± 0.4	1.7 ± 0.5	0.006
Hemoglobin	13.1 ± 1.6	12.3 ± 1.9	0.02
Transplant vasculopathy	7/52 (13%)	29/53 (55%)	0.003
Tricuspid regurgitation	6/52 (12%)	15/53 (28%)	NS
Diastolic dysfunction	1/52 (2%)	9/53 (17%)	0.02
Hypertrophy	21/52 (40%)	25/52 (47%)	NS
Mean pulmonary artery pressure	18.4 ± 4.7	19.5 ± 3.7	NS
Mean blood pressure	97.0 ± 12.5	97.8 ± 10.9	NS
Pulmonary vascular resistance	115.3 ± 52.8	105.2 ± 42.0	NS
DM pretransplant	9/52 (17%)	6/53 (11%)	NS
DM post-transplant	19/52 (37%)	14/53 (26%)	NS
Rejection index	0.44 ± 0.49	0.67 ± 0.60	0.045
CMV infection	13/52 (25%)	15/53 (28%)	NS

Two patient groups were formed according to BNP cut-off level 96.8 pg/ml (median). Clinical, demographic, and hemodynamic parameters for each patient group are shown. Data are presented as the mean ± SD or *n*/*N* (%) of patients, significant differences are indicated by the *P*-value (*t*-test, Mann–Whitney *U*-test or chi-square test as appropriate).

ICMP, ischemic cardiomyopathy; DM, diabetes mellitus; CMV, cytomegalovirus; BNP, B-type natriuretic peptide.

Table 2. Demographic, clinical, and hemodynamic parameters associated with BNP plasma levels in heart transplant recipients.

Determinant	*P*-value
Transplant vasculopathy	<0.0001*
Creatinine	<0.0001*
Hemoglobin	0.0006*
Donor age	0.0007*
Tricuspid regurgitation	0.002*
Female recipient gender	0.006*
Diastolic dysfunction	0.01*
Cyclosporin A	0.02*
Time post-transplant	0.04*
Female donor gender	0.1
Recipient age	0.2
Time of ischemia	0.3
Hypertrophy	0.4
Mean pulmonary artery pressure	0.5
Mean blood pressure	0.6
Ischemic cardiomyopathy	0.6
Gender mismatch	0.6
Diabetes mellitus post-transplant	0.7
Diabetes mellitus pretransplant	0.7
Pulmonary vascular resistance	0.8
Rejection index	0.8
CMV infection	0.95

Univariate statistical regression analysis or Mann–Whitney *U*-test was performed as appropriate to determine the influence of several clinical, demographic, and hemodynamic variables on BNP plasma levels. *P*-values are illustrated for each variable tested. The asterisk indicates statistically significant *P*-values (<0.05).

CMV, cytomegalovirus; BNP, B-type natriuretic peptide.

Univariate analysis identified clinical, demographic, and hemodynamic variables for BNP plasma levels (Table 2). Angiographic signs of TVP ($P < 0.0001$), elevated serum creatinine levels ($P < 0.0001$), low hemoglobin levels ($P = 0.0006$), donor age ($P = 0.0007$), tricuspid regurgitation ($P = 0.002$), female recipient gender ($P = 0.006$), diastolic dysfunction by echocardiographic measures ($P = 0.01$), cyclosporin A levels ($P = 0.02$), and time post-transplant ($P = 0.04$) as clinical, demographic or hemodynamic parameters were significantly associated with BNP plasma levels. No correlation was found with acute rejection, female donor gender, recipient age, time of ischemia, left ventricular hypertrophy, mean pulmonary artery pressure, mean blood pressure, ischemic cardiomyopathy, gender mismatch, diabetes mellitus pre- and post-transplant, pulmonary vascular resistance, rejection index, and CMV infection.

Parameters found to be at least weakly correlated with BNP plasma levels by univariate analysis were included in multivariate logistic regression analysis (Table 3). Here, female recipient gender ($P = 0.006$, 95% CI: 2.04–69.95), time post-transplant ($P = 0.006$, 95% CI: 1.000–1.001), donor age ($P = 0.007$, 95% CI: 1.021–1.14), TVP by angiographic diagnosis ($P = 0.03$, 95% CI: 1.13–13.25), and serum creatinine levels ($P = 0.04$, 95% CI: 1.1–28.59) were found to be independently correlated with BNP plasma levels.

While donor gender and gender mismatch or ischemic time had no appreciable independent impact on BNP plasma levels, the combination of donor age and time after transplantation (i.e. the total age of the graft) was even more strongly associated with BNP plasma levels than either parameter alone ($P = 0.0051$, 95% CI: 1.02–1.14).

Table 3. Independent parameters determining BNP plasma levels in heart transplant recipients.

Determinant	*P*-value
Female recipient gender	0.006 *
Time post-transplant	0.006*
Donor age	0.007 *
Transplant vasculopathy	0.03*
Creatinine	0.04*
Diastolic dysfunction	0.09
Hemoglobin	0.1
Recipient age	0.2
Cyclosporin A	0.4
Tricuspid regurgitation	0.4
Donor gender	0.97

Multiple logistic regression analysis was performed including determinants of B-type natriuretic peptide (BNP) plasma levels in heart transplant recipients showing *P*-values <0.25 by univariate analysis. All determinants included in multivariate analysis are listed in Table 3, $P < 0.05$ was considered significant indicated by the asterisk.

Discussion

The B-type natriuretic peptide (BNP) is increasingly being recognized as a diagnostic tool in the management of heart transplant recipients. Thus, BNP has been attributed a role in noninvasive monitoring of acute cellular rejection [20] and appears to be a useful marker of hemodynamic alterations and clinical symptoms characteristic of diastolic dysfunction early after heart transplantation [12,13]. The present study examines the influence of a wide range of demographic, clinical, and hemodynamic parameters on BNP plasma levels in the chronic phase after heart transplantation in 105 patients with normal LVEF by echocardiography. Parameters known to be associated with BNP plasma levels in nontransplant patients and those known to have an important impact on outcome after heart transplantation were examined [24]. Multivariate analysis revealed time post-transplant, donor age, female recipient gender, serum creatinine levels, and angiographic signs of TVP to be independently correlated with BNP plasma levels in this group of long-term heart transplant recipients. These findings are in line with published data from chronic heart failure patients showing increased BNP levels in older patients, females [2,14] and patients with renal functional impairment [15,25]. BNP is eliminated from plasma mainly through NP receptors and degraded by neutral endopeptidases but also by glomerular filtration [26–28] explaining the influence of renal function on BNP levels [29]. In contrast, NT-proBNP clearance appears to occur primarily by glomerular filtration [30] making it a less favorable diagnostic test in the transplant population with a high prevalence of renal dysfunction because of prolonged use of immunosuppressive drugs. Furthermore, these data comprehensively characterize determinants of BNP levels in the chronic post-transplant phase extending the recently published finding of a correlation between time post-transplant and serum creatinine levels with NT-proBNP in a smaller number of patients using a different assay (NT-proBNP) [31].

The cardiac transplant setting offers the unique possibility to separately analyze the influence of the donor organ and the recipient host organism on the regulation of BNP plasma levels. Interestingly, in the current study the age of the donor organ but not donor gender influenced BNP levels. Gender mismatch was also not significantly associated with BNP. As recipient gender, however, had a major impact on BNP levels it appears that increased BNP levels in females may occur not by way of differences in cardiac release but rather by variations in metabolism/excretion as renal function was not worse compared with male recipients (data not shown). This concept is underscored by a recent report showing an increase of BNP levels upon supplementing female gonadal hormones during hormone replacement therapy in postmenopausal women [32]. Recent animal data have shown that the NP system is expressed in the female reproductive tract (ovaries) and is modulated by estrogen [33]. In addition, estrogen receptors in the rat heart were shown to activate atrial natriuretic peptide (ANP). In that study, decreased ANP production (atrial tissue and plasma) occurred after ovarectomy, which could be restored upon estrogen supplementation and was accompanied with a decrease in heart rate [34]. Similarly, hormone replacement therapy in women has been shown to increase NT-proANP levels [35]. To our knowledge, there are currently no data available showing a similar link for cardiac BNP production and estrogen. With our data, the transplant situation appears to be an appropriate setting to help clarify the origin of estrogen-modulated BNP production (gonadal versus cardiac following estrogen stimulation). The effect of time/age, however, appears to reside within the BNP-producing organ itself (here graft), as the strongest association with BNP plasma levels was shown for the combination of donor age and time after transplantation (total graft age).

Rejection history (reflected by a specific rejection index) was not independently correlated with BNP plasma levels in this study looking at patients in the chronic post-transplant phase (>0.75 years post-transplant). Heart transplant recipients in the early post-transplant phase with a higher incidence of rejection, however, appear more appropriate to further evaluate a potential correlation between BNP levels and acute ongoing rejection. Furthermore, regarding the multitude of potentially confounding factors found in this study, serial BNP measurements in individual patients appear to be a more

suitable study design than cross-sectional observation at one time-point to evaluate the role of BNP in transplant-associated disease such as rejection [20].

Hypertension had no significant influence on BNP in this study, however, all patients were on potent antihypertensive drugs effecting adequate control of blood pressure [mean (SD) arterial pressure: 97.4 (11.7) mmHg]. This control of overt hypertension may also account for the lack of a correlation between hypertrophy measured by echocardiography (LV posterior wall and septal thickness) with BNP in this study. However, by univariate analysis factors exerting strain on the ventricular (or atrial) myocardium such as tricuspid regurgitation and anemia were, indeed, significantly associated with BNP. Elevated cyclosporin A levels also correlated with BNP by univariate analysis, however, failed to maintain significance by multivariate analysis. Renal functional impairment represented a major independent predictor of elevated BNP levels, thus elevated cyclosporin A levels might be a contributing factor via deteriorating renal function rather than a significant determinant of BNP levels in itself. Anemia might be envisaged to exert a direct effect upon BNP levels by way of increased cardiac stress through higher required cardiac output. In the present study, however, anemia should more likely be regarded as a consequence of compromised renal function as by multivariate analysis hemoglobin was not independently associated with BNP levels unlike serum creatinine. Previous data from our group support this notion [36].

In the late phase, after heart transplantation myocardial hypertrophy and fibrosis are a frequent finding [16] indicating a poor outcome [19]. Several factors are implicated in the pathogenesis of myocardial hypertrophy and fibrosis after heart transplantation including hypertension [18] and the development of TVP [19] by means of microinfarctions. Interestingly, in our study the presence of angiographic signs of TVP was independently correlated with increased BNP plasma levels. However, in light of the multitude of other factors influencing BNP levels arguing for intraindividual rather than interindividual comparison of BNP levels in heart transplant recipients the current study was not adequately designed to sufficiently interpret this intriguing finding. Furthermore, as BNP levels appear to increase with time post-transplant the delay (mean ± SD: 0.6 ± 0.88 years) between angiographic diagnosis of TVP and subsequent BNP measurement yielding elevated BNP levels may have led to this increase rather than TVP itself.

Limitations of this cross-sectional observational study result from the single center approach including small number of patients. The patient population examined was characterized by a heterogeneous immunosuppressive regimen, however, this appears to be representative of current practice at other centers and no significant differences were found in the patient group with high BNP levels compared to the group with low BNP levels (using the median as a cut-off). By way of exclusion criteria all patients had a good systolic LV function (LVEF ≥ 40% on echocardiogram) as the aim of this study was to evaluate determinants of BNP levels in clinically stable patients in the absence of LV dysfunction. However, two patients presenting to our institution outside of this study with acute allograft failure and reduced LV function (LVEF < 30%) (due to acute cellular rejection with hemodynamic compromise) showed a dramatic increase in BNP plasma levels (>1300 pg/ml). This anecdotal report is confirmed by recent data on 60 patients demonstrating the ability of serial and rapid elevation of BNP levels to predict cardiac allograft failure requiring hospitalization [37] and may provide a causal link to the reported elevation of BNP with graft rejection [20]. In order to avoid early perturbations of BNP levels possibly related to perioperative stress only long-term heart transplant recipients were examined as previous data show a transient reduction of BNP early after heart transplantation [38].

In the present cross-sectional observational study, we show that BNP plasma levels in the chronic phase after heart transplantation are influenced by several factors. Similar to the nontransplant setting female gender and renal functional impairment are closely associated with elevated BNP plasma levels after heart transplantation. The unique transplant situation sheds new light on BNP regulation, suggesting a gender effect via altered metabolism rather than different cardiac release. Furthermore, BNP plasma levels appear to be significantly influenced by transplant-specific determinants such as donor age and time post-transplant. The data also imply a potential association of BNP plasma levels with the presence of TVP. From our data, it appears appropriate to prefer serial intraindividual measurements of BNP plasma levels over interindividual comparisons at one time-point in future studies in order to evaluate BNP as a potential surrogate marker of cardiac allograft dysfunction.

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