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ORIGINAL ARTICLE

Endocrine heart after lung transplantation: increased brain natriuretic peptide is related to right ventricular function

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Summary

Brain natriuretic peptide (BNP) increases in proportion to the extent of right ventricular dysfunction in pulmonary hypertension and after heart transplantation. No data are available after lung transplantation. Clinical, biological, respiratory, echocardiographic characteristics and circulating BNP and its second messenger cyclic guanosine monophosphate (cGMP) were determined in thirty matched subjects (10 lung-, 10 heart-transplant recipients (Ltx, Htx) and 10 healthy controls). Eventual correlations between these parameters were investigated. Heart rate and pulmonary arterial blood pressure were slightly increased after transplantation. Creatinine clearance was decreased. Mean of forced expiratory volume in 1 s was 76.6 ± 5.3% and vital capacity was 85.3 ± 6.4% of the predicted values in Ltx. BNP was similarly increased in Ltx and Htx, as compared with control values (54.1 ± 14.2 and 45.6 ± 9.2 vs. 6.2 ± 1.8 pg/ml, respectively). Significant relationships were observed between plasma BNP and cGMP values ($r = 0.62$; $P < 0.05$ and $r = 0.75$; $P < 0.01$, in Ltx and Htx) and between BNP and right ventricular fractional shortening and tricuspid E/Ea ratio in Ltx ($r = -0.75$ and $r = 0.93$; $P < 0.01$, respectively). BNP is increased after lung transplantation, like after heart transplantation. The relationships observed suggest that the cardiac hormone might counterbalance possible deleterious effects of lung-transplantation on right functioning of patient's heart.

Introduction

Lung transplantation has become a realistic therapy for patients with end-stage pulmonary disease. Indeed, major advances in organ preservation, surgical procedures, immuno-suppression, and antibiotic therapy contribute significantly in both short-term and long-term survival and quality of life of patients with lung transplantation (Ltx). All recipients confounded the 1, 5, and 10 year survival rates after lung transplantation average respectively around 80%, 60%, and 30%. Infection, secondary malignancy, and renal dysfunction – likely related to immunosuppressant toxicity – are frequent complications after lung transplantation, but lung rejection leading to bronchiolitis obliterans onset and development remains the main cause of morbidity and mortality [1–4].

Brain natriuretic peptide (BNP) is a cardiac hormone acting through its second messenger cyclic guanosine monophosphate (cGMP) and the relationship between BNP and cGMP has been viewed as an index of the biological activity of BNP [5]. BNP has powerful diuretic, natriuretic, lusitropic and vasodilatory properties. Thus, BNP plays a major role in blood pressure and fluid homeostasis, protecting the heart from volume and pressure overloads. Accordingly, BNP is now considered as a compensatory mechanism delaying the occurrence of

overt heart failure and it is widely used for diagnostic, prognostic and even therapeutic purposes in patients presenting with left heart impairment [6–10]. Like atrial natriuretic peptide, increased BNP has also been consistently reported after heart transplantation, mainly in relation with altered cardio-renal function and/or pulmonary hypertension and it has been shown to have significant beneficial biological effects [6,8,11–16].

Concerning respiratory disease, there is good evidence that BNP has a diagnostic role and might help stratify the risk in patient with right ventricular overload and pulmonary hypertension. Thus, BNP increases in proportion to the extent of right ventricular dysfunction in pulmonary hypertension and elevated BNP identified a subset of patients with acute pulmonary embolism at higher risk of adverse outcome [17–22]. Natriuretic peptide use should also show some benefits in patients with lung disease as it reduces pulmonary vascular resistance, delays pulmonary hypertension progression and reduces cardiac hypertrophy [23]. Nevertheless, although atrial natriuretic peptide attenuates warm ischemia-reperfusion injury in lung [24], to the best of our knowledge, the endocrine heart response to lung transplantation remains unknown.

The aim of this pilot study was therefore to determine the circulating BNP and cGMP values after lung transplantation, to compare them to values obtained in matched heart-transplanted patients (Htx) and healthy controls and to challenge the hypothesis that BNP might be increased in Ltx recipients in relation with their right heart function.

Methods

Subjects

Thirty age- and body mass index-matched subjects, 10 stable Ltx, 10 stable Htx and 10 healthy controls, gave informed consent and participated in this study, which was approved by the Institutional Review Board for Human Studies. All subjects were in sinus rhythm. All, but one Ltx (demonstrating rejection 2 months before the study and going well thereafter), were free of cardiac and respiratory reject.

Lung-transplant recipients (five with unilateral and five with bilateral lung transplantation) received immunosuppressive therapies including cyclosporine ($n = 7$), tacrolimus ($n = 3$), mycophenolate mofetil ($n = 5$), azatioprin ($n = 5$) and corticosteroids ($n = 8$). Concomitant treatments consisted of statins ($n = 9$) and anti-hypertensive treatment such as angiotensin-conversion enzyme inhibitors (ACEI, $n = 4$), calcium antagonists ($n = 4$), beta-blockers ($n = 1$) and/or diuretics ($n = 1$). One control was under low dose beta-blockers for a light well-controlled hypertension.

Study design

After an overnight fast, before any medication administration, each subject underwent physical examination and a complete cardiac echodoppler analysis. Within a delay of 15 min, a blood sample for biological and hormonal determinations was drawn from a peripheral antecubital vein. All procedure took place between 8 a.m. and 9 a.m to avoid eventual circadian variations. As BNP levels might not be very stable immediately post-transplant, we determined the cardiac hormone values later during the usual follow-up in stable consecutive subjects. The time interval between transplant and BNP measurements was 30.5 ± 12.7 and 80.2 ± 18.8 months after lung and heart transplantation, respectively.

Parameters determined

Hemodynamic parameters

Systemic blood pressure was determined with the oscillometric method using a tensiometer (Critikon, Paris, France). Heart rate was obtained simultaneously.

Doppler echocardiography

Doppler echocardiograms were performed according to the American Society of Echocardiography Recommendations in all patients, using an ATL HDI 5000 echocardiography (Bothell, WA, USA) equipped with a 2.5-MHz transducer. Echocardiographic examination included analyses of left and right ventricle (LV and RV), systolic and diastolic functions, using two-dimensional and M-mode examinations, Doppler and tissue Doppler imaging (DTI).

Mitral and tricuspid flows were recorded with a pulsed-wave Doppler from the apical 4-chamber view, placing the sample volume at the tips of the open valve leaflets. Measured parameters included maximal Doppler velocity of early inflows (E wave), late inflows (A wave), and E/A ratios at both the mitral and tricuspid sites. Early diastolic velocities of the mitral and tricuspid annulus (Ea) were also measured with Doppler Tissue Imaging at the lateral annulus from the apical 4-chamber view, determining noninvasively the pulmonary capillary and right ventricular filling pressures, respectively [25]. All right heart Doppler flows were recorded in the tele-expiratory time.

The systolic pulmonary arterial pressure (sPAP) was assessed by continuous-wave Doppler localized on tricuspid regurgitation flow and the right atrial pressure was estimated by analyzing the inferior vena cava diameter. Each Doppler measurement at a given site was performed over three consecutive cardiac cycles, and the results were averaged.

Respiratory parameters

Flow-volume curves were measured using a MS-PFT device (Jaeger USA Masterscreen Diffusion TP, VIASYS Healthcare) and following the ATS/ERS recommendations [26]. Reference equations were those published by the ERS [27].

Measurements of biological parameters and hormones plasma levels

Blood was drawn into tubes prepared with ethylenediamine tetraacetic acid (EDTA) and aprotinin. The samples were chilled with ice and immediately centrifuged for 15 min at 1000 *g* and 4 °C, and then stored at −80 °C until analysis.

Blood and urinary creatinine were measured using an automat (ADVIA 1650, Siemens Medical Solutions, Erlangen, Germany) and creatinine clearance was used to determine the subjects renal function.

Plasma BNP (Shionoria kits, distributed by Cis Bio International, Gif-sur-Yvette, France), cGMP (Beckman Coulter, Villepinte, France) levels were determined by radioimmuno assays, as previously reported. BNP detection limit was 2.0 pg/ml, cGMP detection limit was 10 pmol/l. All samples from one individual were analyzed in a single series and intra-assay coefficients of variation were less than 5%.

Statistical analysis

Results are expressed as mean ± SEM. Comparisons between groups were performed by using one-way analysis of variance following, where needed, by *a posteriori* Tukey's test. Relationships between two groups of variables were assessed by calculating Pearson correlation coefficient. Statistical significance required a $P < 0.05$.

Results

The clinical and biological characteristics of the controls, lung and heart-transplant recipients are presented in Table 1.

The three groups were matched for age and body mass index. The heart rate was significantly higher in lung and heart transplant recipients than in controls. Mean systemic arterial pressure was similar in the three groups of subjects. Creatinine clearance was similarly decreased in both transplant groups and cyclosporinemia was increased in lung, as compared with heart transplant recipients.

The left and right heart systolic and diastolic characteristics of the three groups are displayed on Table 2 and Fig. 3.

Table 1. Clinical and biological characteristics of the controls, lung and heart-transplant recipients.

	Controls	Lung transplants	Heart transplants
Age (years)	48.3 ± 2.1	45.8 ± 3.8	45.4 ± 3.3
BMI (kg/m^2)	24.7 ± 1.3	23.6 ± 1.2	26.8 ± 1.7
Gender	5 M/5 F	8 M/2 F	8 M/2 F
Heart rate (bpm)	61.4 ± 2.4	80.5 ± 4.5**	76.6 ± 3.6*
Mean AP (mmHg)	96.1 ± 2.6	101.0 ± 2.4	106.7 ± 4.4
Creatinine clearance (ml/min)	100 ± 7.0	65 ± 4.6**	70 ± 7.2**
Cyclosporinemia (ng/ml)		206.4 ± 36.4	108.4 ± 10.9††

Mean ± SEM. BMI, body mass index; AP, systemic arterial pressure.
Difference with controls: *$P < 0.05$; **$P < 0.01$.
Difference with lung transplants: ††$P < 0.01$.

Table 2. Left and right heart systolic and diastolic characteristics of the three groups.

	Controls	Lung transplants	Heart transplants
LV-FS (%)	37.7 ± 1.3	35.2 ± 1.2	37.5 ± 1.8
RV-FS (%)	54.0 ± 4.3	59.3 ± 3.6	52.1 ± 4.6
Mitral E/A ratio	1.24 ± 0.08	1.29 ± 0.22	2.03 ± 0.17**,†
Mitral E/Ea ratio	5.34 ± 0.51	5.08 ± 0.73	4.91 ± 0.25
Tricuspid E/A ratio	1.96 ± 0.15	1.15 ± 0.07**	1.60 ± 0.09†
Tricuspid E/Ea ratio	3.46 ± 0.26	3.92 ± 0.45	5.72 ± 0.55**,†
Systolic PAP (mmHg)	19.5 ± 1.5	27.3 ± 2.0*	27.6 ± 1.8*

Mean ± SEM. LV-, RV-FS left and right ventricular fractional shortening; E and A, mitral and tricuspid early and late diastolic velocities; Ea, lateral mitral and tricuspid annulus early diastolic velocity; PAP, pulmonary arterial pressure.
Difference with controls: *$P < 0.05$; **$P < 0.01$.
Difference with lung transplants: †$P < 0.05$.

Echocardiographic left and right ventricular fractional shortening were in the normal range and did not differ significantly among the three groups.

Similarly, although lung and heart-transplant recipients showed a trend toward a mitral restrictive pattern (increased mitral E/A ratio) and toward an altered RV relaxation (reduced tricuspid E/A ratio), their cardiac diastolic function remained in the normal range. Accordingly, when analyzing the whole group, the mitral and tricuspid E/Ea ratio – reflecting respectively the LV and RV end-diastolic pressures – showed normal values. Selected individual data are presented in Fig. 3.

Finally, the systolic pulmonary artery pressure – estimated from tricuspid regurgitation flow- and vena cava reactivity – in 21 of the 30 subjects was similarly

increased in lung and transplant recipients as compared with controls, but such increase was very mild.

Respiratory characteristics of the lung-transplant recipients

The mean of Forced Expiratory Volume in one-second (FEV1) expressed as percentage of predicted value was 76.6 ± 5.3%. The vital capacity (VC) was 85.3 ± 6.4% of the predicted value and the FEV1/VC ratio was 72.6 ± 5.6% of normal values. FEV1 was decreased in unipulmonary as compared with bipulmonary lung transplant recipients (61.2 ± 4.3 vs. 86.0 ± 5.6%, $P = 0.008$).

Brain natriuretic peptide is increased similarly in lung and heart-transplant recipients

Figure 1 outlines the plasma levels of BNP and cyclic GMP in the three groups. Circulating BNP was significantly higher in lung and heart transplant patients than in controls (54.1 ± 14.2, 45.6 ± 9.2 and 6.2 ± 1.8 pg/ml, respectively). BNP was not significantly different in unilateral versus bilateral lung-transplant recipients.

Plasma cGMP levels failed to differ significantly between the three groups, even if levels were higher in lung and heart transplant patients (9.7 ± 1.0, 8.8 ± 1.4 and 5.9 ± 0.9 nmol/l, respectively).

Table 3. Lung-transplant recipients' preoperative diagnosis and mean brain natriuretic peptide values.

Cystic fibrosis	$n = 3$	BNP 17 pg/ml
Bronchiolitis postmarrow allograft	$n = 1$	BNP 24 pg/ml
Emphysema	$n = 2$	BNP 58 pg/ml
Nonspecific interstitial pneumopathy	$n = 1$	BNP 59 pg/ml
Congenital cardiomyopathy	$n = 1$	BNP 83 pg/ml
Idiopathic pulmonary fibrosis	$n = 2$	BNP 101 pg/ml

n, number of patients.

Taking into account the preoperative diagnosis, BNP appeared to be more increased in patients suffering initially from idiopathic pulmonary fibrosis, congenital cardiomyopathy with Eisenmenger, nonspecific interstitial pneumopathy, and emphysema (Table 3). These patients presented with more elevated RV pressures, as inferred from their tricuspid E/Ea ratio (Fig. 3).

As displayed on Fig. 2, significant relationships were observed between plasma BNP and cGMP values, both in lung and in heart transplant patients ($r = 0.62$; $P < 0.05$ and $r = 0.75$; $P < 0.01$, respectively). The two patients presenting with BNP values higher than 100 pg/ml demonstrated reduced right ventricular fractional shortening

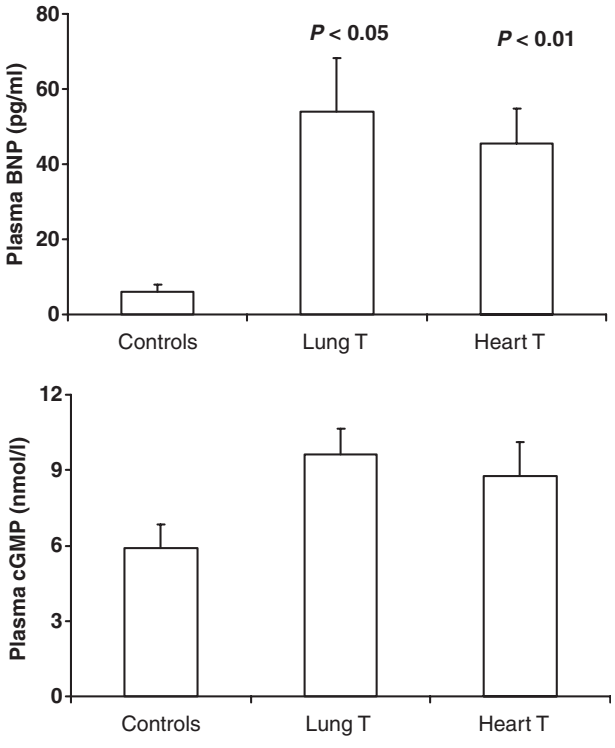

Figure 1 Circulating brain natriuretic peptide and cyclic guanosine monophosphate in healthy subjects, lung and heart-transplant recipients.

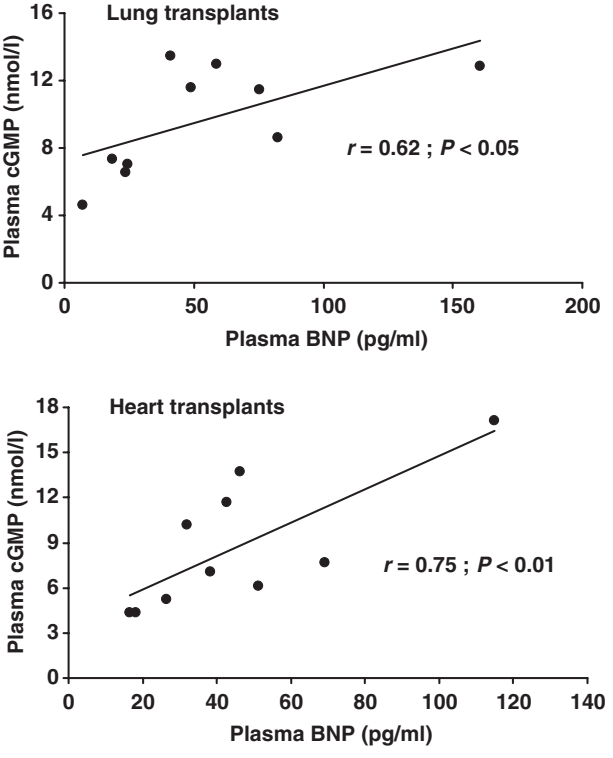

Figure 2 Relationships between circulating brain natriuretic peptide and cyclic guanosine monophosphate in lung and heart-transplant recipients.

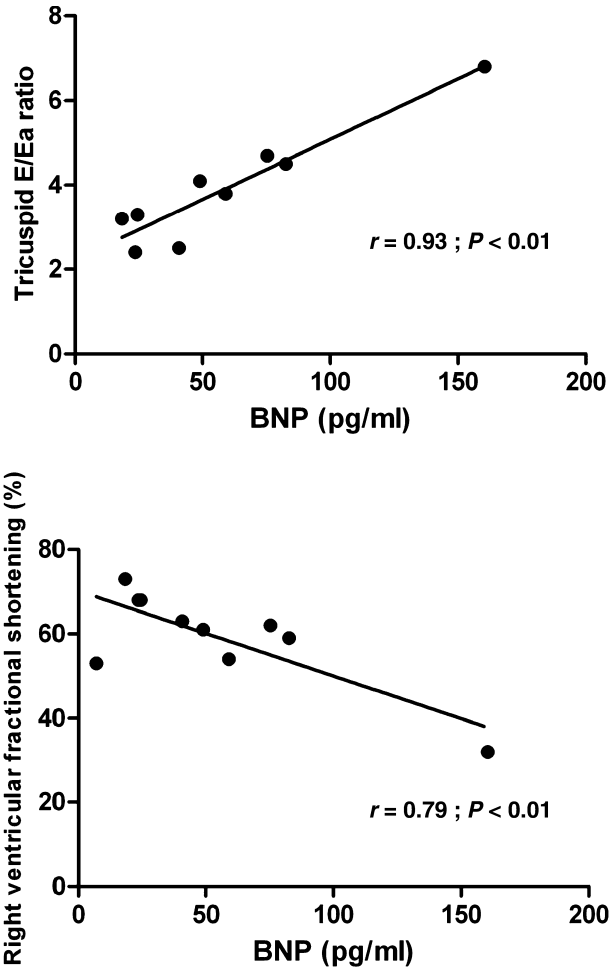

Figure 3 Relationships between circulating brain natriuretic peptide and right ventricular fractional shortening and tricuspid E/Ea ratio in lung-transplant recipients.

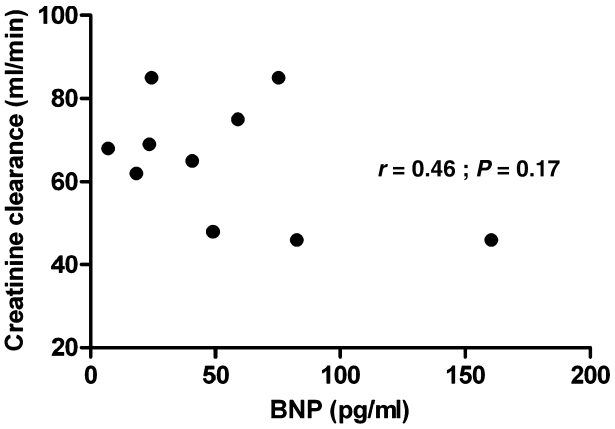

Figure 4 Circulating brain natriuretic peptide and creatinine clearance in lung-transplant recipients.

and increased tricuspid E/Ea ratio as compared with the mean values of the entire groups (32 and 39% for RV-FS and 6.8 and 6.6 for tricuspid E/Ea ratio, for the lung- and the heart-transplant recipient, respectively).

In lung transplant patients, significant relationships were also observed between plasma BNP levels and right ventricular fractional shortening ($r = -0.75$; $P < 0.01$) and with tricuspid E/Ea ratio, reflecting the right ventricular pressures ($r = 0.93$; $P < 0.01$), Fig. 3. Circulating BNP tended to be correlated with creatinine clearance in lung-transplant recipients ($r = 0.46$; $P = 0.17$, Fig. 4), but BNP did not correlate with systolic PAP.

Discussion

This study demonstrates, for the first time, that circulating BNP is increased after lung transplantation. Such an increase was similar to that observed after heart transplantation. After lung transplantation, BNP positively correlated with its second messenger cGMP and the greater the BNP values, the lower the RV fractional shortening and the higher the RV pressures.

These data suggest that increased BNP could be biologically active and might counterbalance the possible deleterious effects of lung-transplantation on right functioning of patient's heart.

Increased BNP after heart transplantation

There are many reports demonstrating that circulating BNP is increased after heart transplantation. Although unexpected at first glance, because of the normalization of cardiac filling pressures and of the renin-angiotensin-aldosterone and sympathetic systems after successful transplantation, such cardiac hormone increase is now thought to be mainly related to heart-transplant recipients cardiac and/or renal alterations occurring with time after surgery. Thus, these alterations might be ascribed both to vascular alterations (existing before heart transplantation and enhanced by the immunosuppressive therapy) and to graft impairment secondary to acute or chronic rejection [6,8,12–16]. Nevertheless, interestingly, increased BNP has also been observed in heart-transplant patients with normal left and right heart systolic and diastolic functions, supporting the concept that immunologic stimulation *per se* might be sufficient to enhance BNP production by the heart [28,29].

A positive correlation between cGMP and BNP being generally considered as a good index of the BNP biological effects, several studies investigated the beneficial effects of BNP after heart transplantation and taken together, despite the fact that – like after heart failure and

pulmonary hypertension – renal hyporesponsiveness to the cardiac hormone might occur [5,30], BNP clearly enhanced water and sodium excretion by the kidneys in Htx *via* an increase of cGMP [15].

Increased BNP after lung transplantation

Increased BNP after lung transplantation has not been reported to date. Its origin might result from decreased clearance and/or increased production. There are two main clearance pathways for BNP, the cellular and the enzymatic pathways through respectively C-type receptors and neutral endopeptidase. Lungs do not extract or extract only very small amounts of atrial natriuretic peptide in patients [31], but kidneys are the main organs where BNP might be degraded. Therefore, increased BNP might be related to impaired renal function both after heart or lung transplantation and, adjusting BNP for such clinical covariate might improve its diagnostic performance [32]. However, in this study, heart and lung transplant-recipients demonstrated relatively slight renal alterations and it is unlikely that a decreased renal clearance participated significantly in their increased BNP. Accordingly, as previously reported in Htx [33,34], although BNP tended to be higher in the LTx presenting with the worse renal function, this relationship was not statistically significant. Thus, like in nontransplanted subjects, one might propose that if patient's glomerular filtration rates are higher than 60 ml/min/1.73 m^2, their renal function has probably little influence on their circulating BNP values [35].

BNP being mainly secreted by the heart, and by analogy with data observed in patients with cardiovascular disease, one can propose that increased BNP production after lung transplantation might be related to the patients pulmonary hypertension and/or cardiac function [6,13,17–20]. Concerning pulmonary hypertension, Ltx demonstrated a significant, but moderate increase in systolic pulmonary pressures. However, although widely used for the determination of sPAP, the noninvasive echo-Doppler approach has technical limitations. Thus, it is not feasible in all subjects – whatever their sPAP values – because of an inadequate TR flow. In this study, although sPAP was obtained in 2/3 of the subjects, the small span of sPAP observed might explain the lack of relationship between circulating BNP and pulmonary artery pressure levels. Furthermore, larger studies will help define better the relationship between PAP and BNP after lung transplantation.

Interestingly, circulating BNP correlated negatively with Ltx right ventricular fractional shortening and positively with the tricuspid E/Ea ratio. The greater the BNP values, the lower the RV fractional shortening and higher the RV pressures. Although correlation does not imply causation, this suggests that the BNP increase observed after lung transplantation might be a compensatory mechanism against reduced cardiac function [13,17–20]. Indeed, BNP correlated positively with its second messenger cGMP and such a relationship has been shown to be an index of the cardiac hormone biological activity [5]. These results are in accordance with previous data in pulmonary diseased patients, where increased BNP was observed in proportion to the extent of right ventricular dysfunction in pulmonary hypertension and where elevated BNP was shown to enhance natriuresis, to reduce pulmonary resistance and/or to improve the cardiac function [15,17–20].

In summary, this pilot study shows that circulating BNP and cGMP are increased after lung transplantation in relation to Ltx right heart function. These data support the usefulness of further larger scale studies to determine whether increased BNP might precede clinical signs of impaired cardiac function and whether BNP -like other vasodilatory peptides – [36] might have prognostic or therapeutic values after lung transplantation.

Authorship

PGDM and BG: wrote the paper, designed research/study, performed research/study, collected and analyzed data. ST: designed research/study, performed research/study, collected and analyzed data. IE and AC: wrote the paper, analyzed data. MAW: collected data. GM and RK: analyzed data. FP: designed research/study, analyzed data, wrote the paper.

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