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Changes in plasma B-type natriuretic peptide after allograft renal transplantation

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Abstract

Objective: To investigate the dynamic changes in plasma B-type natriuretic peptide (BNP) after allograft renal transplantation.

Methods: Plasma BNP was measured in 17 patients before and after unilateral allograft renal transplantation (study group) and in 17 age- and sex-matched healthy individuals (control group).

Results: Average BNP level in the study group was significantly higher than the control group before renal transplantation ($P<0.001$). After transplantation, blood pressure was reduced and left ventricular ejection fraction was increased ($p<0.01$). There was also a substantial reduction in plasma BNP and blood creatinine following the surgery ($p<0.001$). Graft dysfunction accompanied by significant rebound in plasma BNP levels was detected in four patients within two weeks of the surgery.

Conclusions: Plasma BNP levels are elevated in patients with chronic renal failure. Allograft renal transplantation significantly reduces BNP. Sudden increases in plasma BNP after the transplantation are associated with allograft dysfunction. Together with other biomarkers, plasma BNP may be used to predict the changes in renal function after transplantation.

Key words: renal transplantation; BNP; kidney.

Introduction

B-type natriuretic peptide (BNP) is a 32-amino acid peptide mainly synthesized and released from ventricular myocyte in response to increased stress on ventricular wall [1]. Recent studies have demonstrated that BNP is a sensitive and specific biomarker for both systolic and diastolic heart failure [2-4]. Plasma BNP has also been shown to predict the short- and medium-term prognosis of patients with acute coronary syndrome [5-7].

Plasma BNP levels are also elevated in patients with chronic renal failure; every 10 ml/min reduction in glomerular filtration rate corresponds to about 21% increase in plasma BNP [8]. Plasma levels of BNP are often reduced after haemodialysis [9-11]. Renal transplantation also reduces elevated plasma BNP in patients with chronic renal failure [9]. However, the dynamic changes in plasma BNP after renal transplant are unclear. More importantly, whether there is a difference in plasma BNP between patients with and without graft dysfunction secondary to drug toxicities or allograft rejection is unknown. The primary purposes of this study were to investigate the levels of plasma BNP within the first three months of renal transplantation, and to explore the changes of BNP in patients who had experienced post-transplant renal dysfunction.

Patients and methods

Patient selection

This study was approved by the Institutional Review Board of Lishui City Central Hospital, and the study protocols adhered to the *Declaration of Helsinki*. Informed consent was obtained from all participants before the study. Between January 2005 and February 2006, 17 patients undergone living allograft renal transplantation were recruited into this study. There were 5 males and 12 females, with an average age of 44.2±10.0 (range, 30-61) years. All patients had end-stage renal failure as a result of chronic glomerulonephritis, requiring haemodialysis 2-3 times a week. None had concurrent illnesses such as infection, cardiovascular or respiratory diseases, thyroid dysfunction or cancer. Echocardiographic examination 24 h after the last haemodialysis revealed normal cardiac structure and function.

HLA-matched, unilateral allograft renal transplantation was successfully performed in all patients.

Seventeen age- and sex-matched healthy subjects were also recruited from the hospital clinic to serve as controls. Physical and laboratory examination in these subjects was conducted to exclude chronic illnesses such as cardiovascular, renal, thyroid and respiratory diseases.

BNP measurement

We have previously reported the methods for BNP measurement [4]. In the study group, venous blood was collected the day before, daily within 2 weeks of the

surgery, and at the end of 3 months of the operation, respectively. In the control group, venous blood was collected only once for a single BNP measurement.

Blood samples were kept in EDTA tubes at room temperature and analyzed within 4 hours after the collection. Plasma BNP was measured with microparticle enzyme immunoassay (AxSYM® BNP, Abbott Diagnostics, Illinois, USA). If patients were experiencing acute renal rejection, more frequent BNP measurements were conducted.

Diagnosis of allograft dysfunction

Allograft dysfunction was diagnosed when one or more of the following criteria were met, after excluding other causes: 1) sudden reduction in urine volume by more than 30%, which was unresponsive to full dose of frusemide; and 2) an increase in blood creatinine by more than 25% of the baseline. The above clinical and laboratory findings were sometimes accompanied by proteinuria or haematuria, and elevation in blood leucocytes in particular lymphocytes. Renal allograft biopsy was not performed in the suspected patients.

Immunosuppression

Immunosuppression after the transplant was a standard triple therapy, which consisted cyclosporine (75-100 mg, orally, twice a day), mycophenolate mofetil (500-750mg, orally, twice a day) and methylprednisolone sodium succinate (400-500 mg iv on day 1, 300-420 mg iv, on day 2 and 3, replaced by oral prednisolone 80-100

mg per day from day 4 and tapered to 25-30 mg per day over two weeks). The blood concentration of cyclosporine was not monitored.

In our experiences, most patients with acute clinical symptoms of allograft dysfunction were due to acute rejection. Therefore these suspected cases were treated with intravenous infusion of methylprednisolone (500 mg per day for 3 days). Oral dose of cyclosporine was also increased to 125-175 mg twice a day, whereas mycophenolate mofetil was increased to 1,000 mg, orally, twice a day, for 5 days.

Statistical analysis

Data were expressed as means $\pm$ SD. Data analysis was performed with SPSS10.0 software. Comparison of BNP, creatinine and other clinical or laboratory parameters before and after surgery, and between the study and control groups, was performed with student t test or Friedman test where appropriate. $P<0.05$ was considered to be statistically significant.

Results

General findings

Table 1 shows the changes in blood pressure, left atrial diameter, thickness of the inter-ventricular septum and left ventricular posterior wall, left ventricular end-diastolic diameter, left ventricular ejection fraction and blood creatinine, before and after the surgery. There was significant reduction in blood pressure, left ventricular end-diastolic diameter and blood creatinine after the renal transplant

(Table 1, all P <0.05). Left ventricular ejection fraction was also increased (Table 1, p<0.001).

Effect of renal transplant on plasma BNP

Before surgery, the average plasma BNP in patients with renal failure was significantly higher than that of the healthy subjects (644.9±738.4 vs 15.3±18.9 pg/ml, P<0.001).

Plasma BNP was reduced in all patients within 24 h after the surgery. In the 13 patients who did not experience post-surgery allograft dysfunction, the average plasma BNP declined from 504.8 to 311.8 pg/ml 3 days after the surgery (Table 2). Further reduction in BNP was observed in these patients 3 months later (Table 2). Friedman test was used to compare the average BNP levels before, and at various time points after the surgery, showing a significant reduction in BNP from day 1 of the surgery (X^2=14.25，P=0.027).

Four patients were clinically diagnosed with allograft dysfunction. Details of these patients were shown in Table 3.

In patient 4, significant creatinine elevation was noted on day 9 after the transplantation. In this patient, however, BNP was increased on day 4, from 470.1 to 2,347.7 pg/ml (Fig 1 and 2). There were no significant clinical symptoms of allograft dysfunction or acute rejection between day 4 and day 8 in this patient, therefore no adjustment on immunosuppression therapy was made until day 9, when plasma BNP reached 4,000.0 pg/ml (Fig 2). Significant increase in blood creatinine

was also recorded on day 9 (Fig 1). Intravenous methylprednisolone was initiated, resulting in a gradual reduction in BNP and creatinine, and an increase in urine volume after 24 hours (Table 2).

In patient 1, significant reduction in urine volume and elevation of creatinine (less than 25%) occurred on day 12, but significant BNP increase was recorded on day 11 (Fig 1 and 2). In the other 2 patients, significant elevation of blood creatinine and plasma BNP was recorded on day 8 (Fig 1 and 2). In patient 2, there was rebound of both blood creatinine and plasma BNP on day 15 (Fig 1 and 2).

Correlation between creatinine and plasma BNP before and after the surgery in patients with allograft dysfunction

The association between blood creatinine and plasma BNP was analysed before transplantation, and on the day when allograft dysfunction had occurred. There was no significant correlation between creatinine and BNP before ($r=0.212$, $P=0.487$) and after the surgery ($r=0.029$, $P=0.971$).

Discussion

BNP is synthesised in the ventricular myocytes as preproBNP, which is enzymatically cleaved to proBNP and released in the form of hormonally active BNP and inactive N-terminal proBNP [12]. The main physiological function of BNP is vasodilatation and natriuresis, reducing the preload of ventricles [12]. BNP is metabolized by 3 different mechanisms: binding to natriuretic peptide receptors,

cleavage and inactivitation by plasma endopeptidases and clearance by normal glomerular filtration processes [2, 13].

Recent studies have shown that chronic renal diseases have significant impact on the plasma levels of BNP. Significant elevation in BNP has been demonstrated in patients with end-stage renal failure [11, 14, 15]. In the present study on patients undergoing renal transplantation for chronic renal failure, the average pre-transplantation BNP was substantially higher than that of the healthy subjects. Since clinical and echocardiographic examination did not reveal any structural or functional problems of the heart in the study group, the pre-transplantation BNP elevation was most likely caused by chronic renal disease or renal failure.

There may be several explanations for the renal disease-induced increase in plasma BNP. First, sodium and water retention during chronic renal failure may increase the left ventricular end-diastolic volume and wall stress, leading to enhanced biosynthesis and secretion of BNP from ventricular myocytes [9]. This is supported by our study that after the renal transplantation, the reduction of plasma BNP coincided with a significant reduction in the left ventricular end-diastolic volume and increase in left ventricular ejection fraction. Second, reduced glomerular filtration rate during chronic renal failure diminishes renal clearance of BNP [9]. Furthermore, the biosynthesis of endopeptidases may be compromised in the presence of renal disease, resulting in decreased degradation of plasma BNP [9].

In the present study, the dynamic changes of BNP are investigated after

successful allograft renal transplantation. In all patients, a significant reduction in BNP was demonstrated 24 h after the surgery. In patients who did not experience allograft dysfunction, plasma BNP levels were more than halved 7 days after the surgery. After a 3-month follow up, the average BNP was still greater than the control group, reflecting the fact that unilateral renal transplantation has improved but has not completely restored the renal function in these patients. Further studies are required to ascertain whether BNP would return to normal range in a longer term.

In the 4 patients who experienced allograft dysfunction, there was a sudden surge in plasma BNP at or before the time of urine volume reduction and elevation of blood creatinine. In one patient, BNP increase was noted 5 days before the changes in urine volume, when the blood creatinine remained unchanged. When enhanced immunosuppression was administered, a rapid reduction of plasma BNP was observed, whereas no regular pattern of decline in blood creatinine was recorded. These data suggest that plasma BNP may be more sensitive than creatinine in reflecting the sudden changes in renal function, and may be used as a predictor for allograft dysfunction.

A potential drawback of the present study is that the cause of allograft dysfunction is unclear. It is likely that acute allograft rejection is responsible for the sudden deterioration of renal function since enhanced immunosuppression improved the allograft function. However, the diagnosis of acute allograft rejection in our study is uncertain without renal biopsy [16]. In addition, N-terminal proBNP is

predominantly eliminated by glomerular filtration; reduction in renal function has more impact on N-terminal proBNP than BNP [8]. Therefore, the levels of N-terminal proBNP, which was not measured in the present study, may be more sensitive than BNP in reflecting the changes in renal function after renal transplantation.

In conclusion, plasma BNP is elevated in patients with chronic renal failure. Allograft renal transplantation results in a significant reduction in BNP from day 1 of the surgery. There is a substantial rebound in BNP levels when allograft dysfunction occurs. In some patients with acute allograft dysfunction, the changes in plasma BNP appear to be several days earlier than blood creatinine. These results indicate that plasma BNP may be used as a sensitive biomarker for the clinical diagnosis of allograft dysfunction after renal transplantation.

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Table 1. Changes in blood pressure, cardiac function and blood creatinine in 17 patients after renal transplant.

	Before	1 month after	2 months after	P value
SBP (mmHg)	143.29 ±18.31	141.53±14.99	128.35±7.49	0.005
DBP (mmHg)	88.59±12.3	93.76±11.13	79.35 ±8.89	0.001
LV diastolic diameter (mm)	50.65±7.13	46.24±10.16	45.00 ±3.20	0.017
LA diameter (mm)	38.00±7.01	35.82±5.69	34.59 ±6.09	0.190
Inter-septum (mm)	11.53±1.87	11.59 ±1.42	11.00 ±2.81	0.610
LV posterior wall (mm)	11.18±1.81	11.47 ±1.55	11.06 ±2.70	0.480
LVEF (%)	60.76±7.98	67.59 ±7.25	69.29 ±5.85	0.001
Blood Cr (μmol/l）	776.69±243.37	92.00±24.72	89.15±22.23	0.000

SBP and DBP: systolic and diastolic pressure; LV and LA: left ventricular and left atrial; LVEF: left ventricular ejection fraction; Cr: blood creatinine

Table 2. Average BNP in 13 patients without allograft dysfunction.

	Mean	Median
Before transplant	504.8±427.6	418.4
After transplant		
Day 1	480.2±502.2*	297.8
Day 2	400.3±398.1*	167.1
Day 3	311.8±233.3*	268.3
Day 7	201.3±150.6*	221.0
Day 14	248.1±287.9*	215.7
3 months	206.0±199.8*	106.1

*: $p<0.01$ compared with pre-transplant value.

Table 3. Major clinical symptoms and laboratory results in patients with allograft dysfunction.

	Patient 1	Patient 2	Patient 3	Patient 4
Time of rejection	Day 12	Day 8	Day 9	Day 9
Symptoms	Urine reduction, fever,	Urine reduction, fever	Urine reduction	Urine reduction
Creatinine changes	From 107.0 to 112.0 mol/l	From 77.0 to 130.0 mol/l	From 117.0 to 146.0 mol/l	From 163 To 179.0 mol/l
BNP changes	From 110.9 to 697.7 pg/ml	108.4 to 1583.5pg/ml	From 465.1 to 658.9 pg/ml	From 470.1 to 4,000.0 pg/ml
Outcomes	Increase in urine volumes in 48 h, creatinine and BNP was 150.0 μmol/l and 106.3pg/ml, respectively in 72 h	Urine volume improved in 48 h; creatinine and BNP was 171.0μmol/l and 764.2pg/ml , respectively, in 72 h	Urine volume improved in 24 h; creatinine and BNP was 133.0μmol/l and 584.8pg/ml, respectively, in 72 h	Urine volume improved in 24 h, creatinine and BNP was 149.0 μmol/l and 1374.3 pg/ml, respectively, in 72 h

Figure legends

Fig 1. Changes in blood creatinine in patients (No1-No4) who had experienced acute allograft dysfunction. D0: the day before renal transplant. D1-D15: the first and 15th day after renal transplant.

Fig 2. Changes in plasma B-type natriuretic peptide in patients (No1-No4) who had experienced acute allograft dysfunction. D0: the day before renal transplant. D1-D15: the first and 15th day after renal transplant.

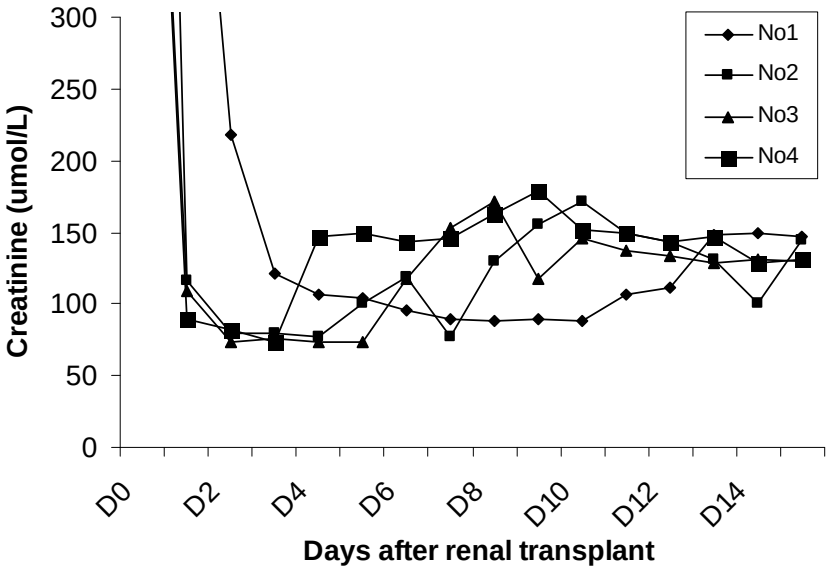

Fig 1

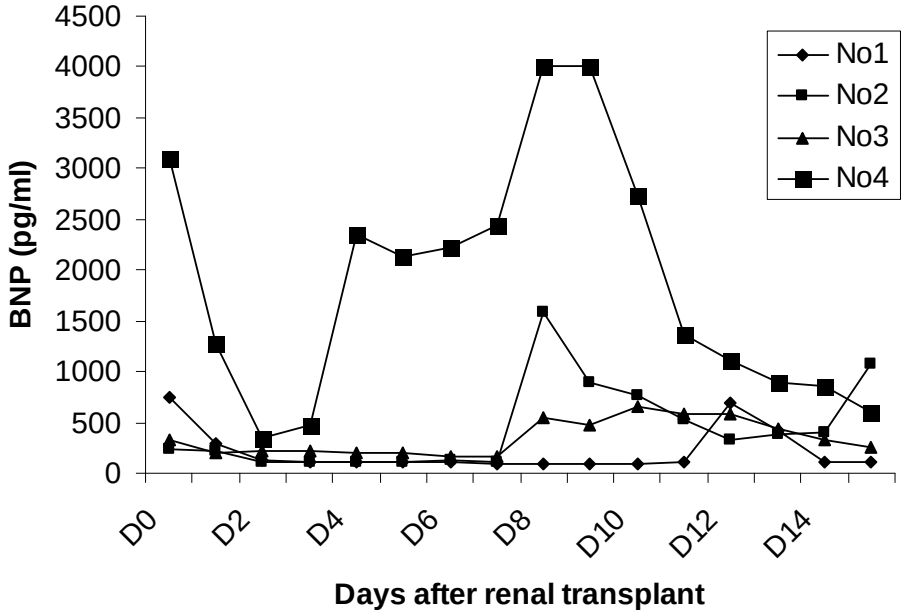

Fig 2