B-type natriuretic peptides are predominantly synthesized in the ventricular myocytes. This is the response to volume overload or increased stress to the ventricular wall. Plasma B-type natriuretic peptide levels are elevated in patients with chronic renal failure due to reduced glomerular filtration and/or increased myocardial biosynthesis. Allograft renal transplantation significantly reduces plasma B-type natriuretic peptide. Our previous clinical observations have demonstrated that acute allograft renal rejection is associated with a sudden increase in plasma B-type natriuretic peptides. We hypothesized that plasma B-type natriuretic peptide may be used as a sensitive and specific biomarker for clinical diagnosis of acute allograft renal rejection.
Plasma B-type natriuretic peptide for early diagnosis of allograft rejection after renal transplantation

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ABSTRACT

B-type natriuretic peptides are predominantly synthesized in the ventricular myocytes. This is the response to volume overload or increased stress to the ventricular wall. Plasma B-type natriuretic peptide levels are elevated in patients with chronic renal failure due to reduced
glomerular filtration and/or increased myocardial biosynthesis. Allograft renal transplantation significantly reduces plasma B-type natriuretic peptide. Our previous clinical observations have demonstrated that acute allograft renal rejection is associated with a sudden increase in plasma B-type natriuretic peptides. We hypothesized that plasma B-type natriuretic peptide may be used as a sensitive and specific biomarker for clinical diagnosis of acute allograft renal rejection.

**Key words:** renal transplantation; B-type natriuretic peptide; acute allograft renal rejection; kidney.
INTRODUCTION

Renal transplantation is one of the most effective treatments for end-stage renal failure. Acute rejection is defined as a sudden deterioration in renal-allograft function. The recipient's immune response to the donor organ is a major risk factor for allograft failure [1, 2]. About 35 percent of allograft recipients have an episode of acute rejection in the first year following transplantation [2]. A needle biopsy of allografts has been used for definitive diagnosis of acute rejection. Needle biopsies are associated with a number of complications, such as hematuria, anuria, perirenal hematoma, bleeding, shock, arteriovenous fistulas, and graft loss [3]. It remains a challenge to develop an accurate and noninvasive diagnostic test for the early diagnosis of allograft rejection.

B-type natriuretic peptide (BNP) is a 32-amino acid peptide mainly synthesized by ventricular myocytes in response to increased stress on the ventricular wall (4). BNP has been used for the diagnosis of systolic and diastolic heart failure [5-7] and to predict the short to medium term prognosis of patients with acute coronary syndrome [8, 9]. 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 [10]. Elevated BNP in renal failure is often reduced after haemodialysis [11]. Renal transplantation also reduces plasma BNP in patients with chronic renal failure [10]. We hypothesize that the levels of plasma BNP after renal transplantation might be used for clinical diagnosis of post-transplant acute renal rejection.

The biosynthesis of BNP

B-type natriuretic peptide (BNP) is synthesized as preproBNP mainly in the ventricular myocardium in response to ventricular stretch and pressure overload [1]. PreproBNP is enzymatically cleaved to proBNP and released in the form of hormonally active BNP and inactive N-terminal proBNP. BNP leads to vasodilatation and natriuresis, which
subsequently results in cardiac preload reduction [12]. Elevated plasma BNP concentrations are often seen in patients with left ventricular dysfunction. The plasma levels of BNP correlate well with pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, and left ventricular ejection fraction in patients with systolic or diastolic dysfunction [5-7]. As a result, BNP has become a valuable diagnostic tool for left ventricular dysfunction in acute and primary care settings [5-7].

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 [15].

**Chronic renal failure and BNP**

Plasma BNP is also elevated in patients with chronic renal failure [11, 13, 14]. The precise mechanisms for BNP elevation in chronic renal failure are unclear but there may be several explanations. Firstly, 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 [10]. Secondly, reduced glomerular filtration rate during chronic renal failure diminishes renal clearance of BNP [10]. Furthermore, the biosynthesis of endopeptidases may be compromised in the presence of renal disease, resulting in decreased degradation of plasma BNP [10].

Several previous studies have shown that renal replacement therapy such as hemodialysis, reduces the levels of plasma BNP [11, 14, 16]. BNP resumes the predialysis level during the dialysis intervals. In our recent studies, progressive reduction in plasma BNP has been found after allograft renal transplantation [17]. For patients who had no acute allograft rejection, plasma BNP levels were more than halved 7 days after the renal transplant and remained low 3 months after the successful transplantation [17].
The mechanisms of BNP reduction after renal replacement therapy are complex and not entirely clear. The dialysis-induced BNP reduction may be due to the restoration of normovolemia and reduction in the ventricular overload [16] but BNP can also be filtered out directly from the blood stream. In our study on renal transplantation, there were no significant changes in left ventricular anatomy and function after the surgery [17]. Therefore the BNP reduction was largely due to the improvement of renal function and elimination of BNP.

**Diagnosis of acute rejection of allograft renal transplantation**

After renal transplantation, acute allograft dysfunction secondary to acute rejection occurs in around 30-40% of patients [1, 2]. Although in the majority of these patients acute allograft dysfunction is reversible, acute rejection remains a major risk factor for the development of chronic rejection. Histology examination of percutaneous needle biopsy is the most accurate diagnostic tool of acute rejection [18]. It does however, have a number of shortcomings such as undesirable complications. Therefore, there has been active research in recent years to develop less invasive procedures that could diagnose rejection and simultaneously provide mechanistic information on the rejection process [18]. The alternative diagnostic procedures that are currently available include duplex Doppler ultrasound assessment, fine-needle aspiration biopsy, urine cytology, urine cytokine analysis, serum cytokine analysis, and cytokine analysis of biopsy material [18].

Since plasma BNP appears to be very sensitive to the variations in renal function, it might be used as a potential biomarker for acute rejection of renal allograft after transplantation. In a recent small-scale clinical study, we found a substantial reduction in plasma BNP 24 hours following surgery [17]. In patients who experience no clinical symptoms of acute rejection, plasma BNP remains low in the first three months of the operation. However, in patients who
had presumptive diagnosis of acute allograft rejection (a more than 25% increase in blood creatinine, fever and/or sudden urine volume reduction), there was a significant rebound in plasma BNP levels at or before blood creatinine elevation [17]. In one patient, BNP rebound was noted 5 days before the occurrence of rejection symptoms, when the blood creatinine remained unchanged [17]. When enhanced immunosuppression was administered to the patients with acute rejection, a rapid reduction of plasma BNP was observed where the decline in creatinine was several days behind the changes in BNP [17]. This data suggests 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 acute allograft rejection.

In conclusion, non-invasive diagnosis of acute allograft renal rejection remains a challenge. Plasma BNP is elevated in patients with chronic renal failure. Allograft renal transplantation results in a significant reduction in BNP. Preliminary clinical observations have found that acute allograft rejection is associated with a significant resurge of plasma BNP, even several days before the increase in blood creatinine. It is likely that BNP, in particular N-terminal proBNP which is predominantly eliminated by glomerular filtration, may serve as a sensitive and specific biomarker for acute rejection. Large-scale clinical studies are required to test this hypothesis.
REFERENCES


