Natriuretic Peptides in Acute and Chronic Kidney Disease and during Renal Replacement Therapy

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ABSTRACT

Plasma levels of natriuretic peptides are elevated in patients with chronic kidney disease owing to impairment of renal function, hypertension, hypervolemia, and/or concomitant heart disease. Proteinuria and/or immunosuppression also contribute to enhanced plasma levels and increased urinary excretion of natriuretic peptides. Atrial natriuretic peptide (ANP) and particularly brain natriuretic peptide (BNP) levels are linked independently to left ventricular mass and function and predict total and cardiovascular mortality. ANP and BNP decrease significantly during hemodialysis treatment but increase again during the interdialytic interval. Intraperitoneal administration of ANP decreases peritoneal fluid and glucose absorption, as well as lymphatic flow rate. Successful kidney transplant normalizes the plasma levels of natriuretic peptides in the majority of patients. In experimental animals but not in humans, ANP administration protects against ischemic acute renal failure. Since proANP31-67 peptide does not cause hypotension, this vessel dilator may protect the kidney during acute renal failure by intrarenal vasodilation and stimulation of endogenous prostaglandin E₂ synthesis.

Key Words: natriuretic peptides, chronic kidney disease, acute renal failure

Cardiac gene expression and secretion of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are stimulated in response to chronic volume and pressure hemodynamic overloads. Mechanical and neurohumoral factors participate in the regulation of natriuretic peptides under these conditions. Patients with chronic kidney disease often suffer from hypervolemia and elevated blood pressure. It is therefore not surprising that the plasma levels of natriuretic peptides are elevated in these patients. In the atria, volume-induced stretch of the atrial muscle

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results in the expression of natriuretic peptides, whereas the endocrine environment is largely responsible for the level of expression in the ventricles.^{2,3}

NATRIURETIC PEPTIDES AND HYPERTENSION

Blood pressure elevation is a major risk factor for progression of chronic kidney disease. Therefore, adequate blood pressure control is a major tool to retard progression of chronic kidney disease. Multiple mechanisms contribute to blood pressure elevation in chronic kidney disease, such as activation of the renin-angiotensin-aldosterone system, the sympathoadrenergic system, and the endothelin system, as well as salt and fluid retention. Endothelin (ET)-1 is not only involved in blood pressure elevation but also plays a prominent regulatory role in the determination of gene expression of natriuretic peptides. This is demonstrated by the animal models of two kidney-one clip (2K-1C) Goldblatt hypertension⁴ and deoxycorticosterone acetate (DOCA) salt hypertension.³ The enhanced ventricular ANP and BNP contents observed in 2K-1C rats were totally prevented by blockade of the ET_A receptor subtype in both right and left ventricles. No modifications, however, were observed in the atrial ANP or BNP contents of 2K-1C rats by ET_A blockade.⁴ Similar findings were observed after ET_A blockade in DOCA salt hypertension.³ These findings confirm the hypothesis that the endocrine environment is responsible for the expression of natriuretic peptides in the ventricles, but pressure and volume overload are responsible for the level of expression in the atria.

NATRIURETIC PEPTIDES AND CARDIOVASCULAR MORBIDITY AND MORTALITY

Extracellular volume expansion, hypertension, and concomitant heart disease, as well as severely reduced or abolished renal clearance, are the main factors for raised plasma ANP and BNP concentrations in patients with endstage renal disease (Table 1), and the plasma concentration of both cardiac peptides declines after ultrafiltration and/or dialysis treatment.^{5–7} In dialysis patients, ANP and BNP plasma concentrations are linked independently to

TABLE 1 Mechanisms for Elevated Plasma Levels of Natriuretic Peptides in Chronic Renal Failure

Reduction in glomerular filtration rate

Reduction of neutral endopeptidase activity in the kidney

Hypertension

Hypervolemia

Congestive heart failure

Cardiomyopathy

Creation of arteriovenous fistula

Proteinuria

Immunosuppression

left ventricular mass and function and predict total and cardiovascular mortality.⁸ BNP has a significantly higher sensitivity (88%) compared with ANP (51%) for the diagnosis of left ventricular hypertrophy, but the positive predictive value of the two peptides is very similar (92% vs 87%, respectively). The negative predictive value of BNP for excluding left ventricular hypertrophy is significantly higher compared with ANP (53% vs 31%). Both natriuretic peptides have a high sensitivity for the detection of left ventricular dysfunction (87% vs 94%), but their positive predictive value is low (25% vs 15%). Both ANP and BNP are very useful for excluding this alteration (negative predictive value 97% vs 96%).⁹ Therefore, measurements of ANP and BNP plasma concentrations may be useful for risk stratification in patients with end-stage renal disease.

Patients with left ventricular hypertrophy have higher plasma ANP levels compared with those without left ventricular hypertrophy. BNP is also increased in hypertension¹⁰ and particularly in hypertensive patients with left ventricular hypertrophy.^{11,12} In hemodialysis patients with hypertension and left ventricular hypertrophy, plasma ANP and BNP levels are also significantly higher compared with those with normotension and without left ventricular hypertrophy.^{13,14} In hemodialysis patients, predialytic levels of proANP₁₋₉₈ are 98-fold, of proANP₃₁₋₆₇ are 56-fold, and of proANP₁₋₃₀ are 35-fold elevated compared with healthy subjects.15 Natriuretic peptides of patients with end-stage renal disease are attributed to body fluid volume and hypertension, as well as to reduction in glomerular filtration rate and to a decreased metabolism of neutral endopeptidase activity in the kidney.14 The contribution of the kidney, however, to the whole metabolic clearance rate of ANP is small (approximately 14%). Therefore, one might suggest that extrarenal factors mainly determine the plasma levels of the ANP fragments. Further, only a small amount of ANP is detected in the dialysis fluid. Thus, the elimination by diffusion across the dialyzer membrane is negligible in maintenance hemodialysis patients. Winters and Vesely found that only 1.5% of proANP₁₋₉₈ and proANP₃₁₋₆₇ was cleared by the dialyzer.¹⁶ We compared

plasma ANP levels before and after regular hemodialysis treatment using dialyzers made of polysulfone versus cellulose triacetate. The decrease in the plasma concentrations of proANP $_{1-30}$, proANP $_{31-67}$, and proANP $_{1-98}$ during hemodialysis treatment was significantly higher with the use of cellulose-triacetate dialyzers than with polysulfone dialyzers, suggesting different adsorption of natriuretic peptides to the dialyzer membrane material. 15,17

Cardiac dysfunction is also associated with higher levels of natriuretic peptide in maintenance hemodialysis patients. Plasma concentrations of ANP, proANP₁₋₃₀, proANP₃₁₋₆₇, and proANP₁₋₉₈ are markedly elevated in hemodialysis patients with cardiac dysfunction before and after hemodialysis compared with those hemodialysis patients with normal cardiac function. Predialytic ANP and proANP levels are markedly higher in those hemodialysis patients with moderate or severe hypertension compared with normotensive or mildly hypertensive hemodialysis patients. However, after hemodialysis treatment, natriuretic peptide levels are comparable between these groups. 15 Surprisingly, there was no correlation between ANP and different proANPs with interdialytic weight gain or volume removal during hemodialysis in both hemodialysis patients with normal cardiac function and those with cardiac dysfunction. Patients with and without episodes of hemodialysis-associated hypotension also did not differ with respect to their ANP and proANPs.¹⁵ On the other hand, plasma BNP levels before and after hemodialysis directly correlate with the degree of body fluid retention in maintenance hemodialysis patients.¹⁸ Lee and colleagues found that inferior cava diameter correlates significantly with postdialytic BNP levels.¹⁹ Predialytic BNP level correlates significantly with postdialytic BNP levels, postdialytic diastolic blood pressure, pulse pressure, and the ratio of extracellular fluid to total-body water. Wallin and colleagues tested whether circulatory performance and serum ANP were related to changes in central blood volume associated with hemodialysis therapy.²⁰ A decrease in weight of 3.8 ± 1.3 kg during hemodialysis resulted in a fall of central blood volume, stroke volume, cardiac output, blood pressure, and serum ANP. Interestingly, 2 hours after hemodialysis treatment, central blood volume recovered to its predialytic level, whereas body weight, plasma volume, stroke volume, blood pressure, and serum ANP remained low. It was concluded that the lack of correlations between central blood volume and circulatory performance and serum ANP suggests increased compliance in central vasculature in response to hemodialysis.20

In hemodialysis patients, cardiac failure could be induced by creation of an arteriovenous fistula for dialysis. However, only a few prospective trials evaluated cardiac performance before and after creation of an arteriovenous fistula. Iwashima and colleagues showed that creation of an arteriovenous fistula has significant effects on cardiac systolic and diastolic performance.²¹ The increase in car-

diac output was associated with elevation of ANP levels (r=.61; p=.01) but not BNP levels, indicating that ANP release was induced by volume loading. Conversely, the increase in the ratio of the peak velocity of early diastolic to atrial filling correlated with BNP levels (r=.60; p=.01) but not ANP levels, indicating that BNP release is stimulated by left ventricular dysfunction. Plasma BNP levels in hemodialysis patients with coronary artery disease are significantly greater than those in hemodialysis patients without coronary artery disease and significantly correlated with left ventricular ejection fraction, end-diastolic volume index, and end-systolic volume index.

In patients with aortic stenosis, plasma levels of natriuretic peptides are related to disease severity^{22,23} and symptomatic status.^{24,25} Aortic stenosis is also a major issue in patients with end-stage renal disease owing to calcification of the aortic valve as a result of secondary hyperparathyroidism and long-term elevation of calcium × phosphorus ion product. Bergler-Klein and colleagues investigated the prognostic value of natriuretic peptides in patients with aortic stenosis and plasma creatinine < 2.5 mg/dL.25 Symptom-free survival at 3, 6, 9, and 12 months for patients with N-terminal BNP < 80 versus \geq 80 pmol/L was 100%, 88 \pm 7%, 88 \pm 7%, and 69 \pm 13% compared with 92 \pm 8%, 58 \pm 14%, 35 \pm 15%, and 18 \pm 13%, respectively. Preoperative N-terminal BNP independently predicted postoperative outcome with regard to survival, symptomatic status, and left ventricular function in these patients with asymptomatic severe aortic stenosis.25 The N-terminal fragments of ANP and BNP are very useful in risk stratification for sudden death and death owing to progressive heart failure in chronic heart failure patients.26

In a subset of 15 dialysis patients without left ventricular hypertrophy or other concomitant diseases, Cataliotti and colleagues did not find an increase in plasma BNP concentration compared with controls, suggesting that end-stage renal disease per se is not responsible for the elevated BNP levels in the majority of dialysis patients. ²⁷ Again, plasma ANP and BNP levels were associated with a greater risk of cardiovascular death. ²⁷ The cutoff levels of ANP and BNP were 58 pg/mL and 390 pg/mL, respectively. The incidence of cardiac events was significantly greater in hemodialysis patients with higher levels of ANP (50.0% vs 0.0%) and BNP (72.7% vs 11.9%) than in those with lower levels of the peptides. ²⁸

ANP ADMINISTRATION IN PERITONEAL DIALYSIS

ANP may significantly increase peritoneal fluid removal and small solute clearance in peritoneal dialysis. Intravenous infusion of ANP increased peritoneal fluid formation in pigs.²⁹ Intravenous use of ANP significantly increased the peritoneal clearances for small solutes and the drainage volume after continuous exchanges in nephrectomized rats.³⁰ High-dose intraperitoneal admin-

istration of ANP (50 $\mu g/kg$) increased intraperitoneal volume and decreased peritoneal fluid and albumin absorption rate, as well as lymphatic flow rate. The dialysate overconcentration ratio of glucose increased also by high-dose intraperitoneal ANP administration. The peritoneal glucose absorption was retarded by adding ANP to peritoneal dialysate, but basic diffuse permeability of the peritoneal membrane was not changed. 31

NATRIURETIC PEPTIDES AND RENAL TRANSPLANT

Successful kidney transplant results in normalization of elevated ANP levels,32,33 whereas nonfunctioning renal allografts continue to have elevated circulating concentrations of ANPs.33 ANP infusion at the time of renal transplant does not appear to have any beneficial effect on the outcome of the renal allograft.³⁴ Immunosuppressive therapy may influence the plasma and urine concentrations of natriuretic peptides. Renal transplant recipients with normal renal allograft function and without proteinuria display threefold higher plasma levels of proANP₁₋₃₀ and 7.5fold higher plasma levels of proANP₃₁₋₆₇ compared with controls. Similarly, 24-hour urinary excretion of proANP₁₋₃₀ and proANP₃₁₋₆₇ was also 2.8-fold and 7.5-fold higher than in controls.³⁵ The cause of the increase in proANP peptides in long-term renal transplant patients with normal graft function is most likely due to prednisone because lowdose glucocorticoids directly stimulate the ANP gene to synthesize proANP₁₋₃₀ and proANP₃₁₋₆₇. Further, there was no evidence of volume overload in these patients. In renal transplant recipients, plasma and urinary proANP₁₋₃₀ and proANP₃₁₋₆₇ increased with the severitiy of the proteinuria (see Table 1). In conclusion, plasma concentration and urinary excretion of proANP $_{1-30}$ and proANP $_{31-67}$ in the late post-transplant period of renal transplant recipients are influenced by renal failure, proteinuria, hypertension, and immunosuppression.35

NATRIURETIC PEPTIDES IN ACUTE RENAL FAILURE

The infusion of ANP^{38–47} or urodilatin^{48–50} attenuated renal tissue damage and preserved the glomerular filtration rate in experimental ischemic acute renal failure (ARF), particularly when given directly into the renal artery.⁴⁷ In humans with ARF, ANP administration did not cause significant improvement in kidney function and did not reduce the need for dialysis or reduce mortality.⁵¹ Adverse events of ANPs, such as hypotension and bradycardia, suggest that ANP may be more harmful than helpful with respect to the treatment of ARF patients.⁵² However, proANP_{1–30} (ie, long-acting natriuretic peptide), proANP_{31–67} vessel dilator, and proANP_{79–98} (ie, kaliuretic peptide) have never caused a hypotensive episode in healthy humans or animals^{53–55} or in humans with sodium and water retention.^{56–58}

Vessel dilator decreased blood urea nitrogen, serum creatinine, and mortality in ARF animals. The glomerulus

and renal tubulus were preserved in ARF animals treated continuously with proANP $_{31-67}$ in contrast to those without vessel dilator. ⁵⁹ ProANP $_{31-67}$ may improve kidney function owing to its ability to cause intrarenal vasodilation and its ability to cause the endogenous synthesis of renoprotective prostaglandin E_2 . ⁶⁰ ProANP $_{1-98}$ on the first day in intensive care unit patients with ARF predicts renal impairment as an independent variable. ⁶¹

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