

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

Walter H. Hörl

## 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 proANP<sub>31-67</sub> peptide does not cause hypotension, this vessel dilator may protect the kidney during acute renal failure by intrarenal vasodilation and stimulation of endogenous prostaglandin E<sub>2</sub> 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.<sup>1</sup> 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

results in the expression of natriuretic peptides, whereas the endocrine environment is largely responsible for the level of expression in the ventricles.<sup>2,3</sup>

## 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 hypertension<sup>4</sup> and deoxycorticosterone acetate (DOCA) salt hypertension.<sup>3</sup> The enhanced ventricular ANP and BNP contents observed in 2K-1C rats were totally prevented by blockade of the ET<sub>A</sub> 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<sub>A</sub> blockade.<sup>4</sup> Similar findings were observed after ET<sub>A</sub> blockade in DOCA salt hypertension.<sup>3</sup> 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 end-stage renal disease (Table 1), and the plasma concentration of both cardiac peptides declines after ultrafiltration and/or dialysis treatment.<sup>5-7</sup> In dialysis patients, ANP and BNP plasma concentrations are linked independently to

*From the Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria.*

*Address correspondence to: Dr. Walter H. Hörl, Division of Nephrology and Dialysis, Department of Medicine III, Währinger Gürtel 18-20, A-1090 Vienna, Austria; e-mail: walter.hoerl@meduniwien.ac.at.*

**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.<sup>8</sup> 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%).<sup>9</sup> 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 hypertension<sup>10</sup> and particularly in hypertensive patients with left ventricular hypertrophy.<sup>11,12</sup> 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.<sup>13,14</sup> In hemodialysis patients, predialytic levels of proANP<sub>1-98</sub> are 98-fold, of proANP<sub>31-67</sub> are 56-fold, and of proANP<sub>1-30</sub> are 35-fold elevated compared with healthy subjects.<sup>15</sup> 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.<sup>14</sup> 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.<sup>5</sup> Thus, the elimination by diffusion across the dialyzer membrane is negligible in maintenance hemodialysis patients. Winters and Vesely found that only 1.5% of proANP<sub>1-98</sub> and proANP<sub>31-67</sub> was cleared by the dialyzer.<sup>16</sup> 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<sub>1-30</sub>, proANP<sub>31-67</sub>, and proANP<sub>1-98</sub> 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.<sup>15,17</sup>

Cardiac dysfunction is also associated with higher levels of natriuretic peptide in maintenance hemodialysis patients. Plasma concentrations of ANP, proANP<sub>1-30</sub>, proANP<sub>31-67</sub>, and proANP<sub>1-98</sub> 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.<sup>15</sup> 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.<sup>15</sup> On the other hand, plasma BNP levels before and after hemodialysis directly correlate with the degree of body fluid retention in maintenance hemodialysis patients.<sup>18</sup> Lee and colleagues found that inferior cava diameter correlates significantly with postdialytic BNP levels.<sup>19</sup> 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.<sup>20</sup> A decrease in weight of  $3.8 \pm 1.3$  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.<sup>20</sup>

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.<sup>21</sup> 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.<sup>21</sup> 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.<sup>18</sup>

In patients with aortic stenosis, plasma levels of natriuretic peptides are related to disease severity<sup>22,23</sup> and symptomatic status.<sup>24,25</sup> 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  $\times$  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.<sup>25</sup> 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.<sup>25</sup> 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.<sup>26</sup>

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.<sup>27</sup> Again, plasma ANP and BNP levels were associated with a greater risk of cardiovascular death.<sup>27</sup> 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.<sup>28</sup>

### 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.<sup>29</sup> Intravenous use of ANP significantly increased the peritoneal clearances for small solutes and the drainage volume after continuous exchanges in nephrectomized rats.<sup>30</sup> 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 over-concentration 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.<sup>31</sup>

### NATRIURETIC PEPTIDES AND RENAL TRANSPLANT

Successful kidney transplant results in normalization of elevated ANP levels,<sup>32,33</sup> whereas nonfunctioning renal allografts continue to have elevated circulating concentrations of ANPs.<sup>33</sup> ANP infusion at the time of renal transplant does not appear to have any beneficial effect on the outcome of the renal allograft.<sup>34</sup> 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 proANP<sub>1-30</sub> and 7.5-fold higher plasma levels of proANP<sub>31-67</sub> compared with controls. Similarly, 24-hour urinary excretion of proANP<sub>1-30</sub> and proANP<sub>31-67</sub> was also 2.8-fold and 7.5-fold higher than in controls.<sup>35</sup> 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 low-dose glucocorticoids directly stimulate the ANP gene to synthesize proANP<sub>1-30</sub> and proANP<sub>31-67</sub>.<sup>36,37</sup> Further, there was no evidence of volume overload in these patients. In renal transplant recipients, plasma and urinary proANP<sub>1-30</sub> and proANP<sub>31-67</sub> increased with the severity of the proteinuria (see Table 1). In conclusion, plasma concentration and urinary excretion of proANP<sub>1-30</sub> and proANP<sub>31-67</sub> in the late post-transplant period of renal transplant recipients are influenced by renal failure, proteinuria, hypertension, and immunosuppression.<sup>35</sup>

### NATRIURETIC PEPTIDES IN ACUTE RENAL FAILURE

The infusion of ANP<sup>38-47</sup> or urodilatin<sup>48-50</sup> 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.<sup>47</sup> 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.<sup>51</sup> 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.<sup>52</sup> However, proANP<sub>1-30</sub> (ie, long-acting natriuretic peptide), proANP<sub>31-67</sub> vessel dilator, and proANP<sub>79-98</sub> (ie, kaliuretic peptide) have never caused a hypotensive episode in healthy humans or animals<sup>53-55</sup> or in humans with sodium and water retention.<sup>56-58</sup>

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<sub>31-67</sub> in contrast to those without vessel dilator.<sup>59</sup> ProANP<sub>31-67</sub> may improve kidney function owing to its ability to cause intrarenal vasodilation and its ability to cause the endogenous synthesis of renoprotective prostaglandin E<sub>2</sub>.<sup>60</sup> ProANP<sub>1-98</sub> on the first day in intensive care unit patients with ARF predicts renal impairment as an independent variable.<sup>61</sup>

## REFERENCES

- de Bold AJ, Bruneau BG, de Bold ML. Mechanical and neuroendocrine regulation of the endocrine heart. *Cardiovasc Res* 1996;31:7-18.
- Ogawa T, Linz W, Stevenson M, et al. Evidence for load-dependent and load-independent determinants of cardiac natriuretic peptide production. *Circulation* 1996;93:2059-67.
- Bianciotti L, de Bold AJ. Effects of selective ET<sub>A</sub> receptor blockade on natriuretic peptide gene expression in DOCA-salt hypertension. *Am J Physiol* 2000;279:H93-101.
- Bianciotti LG, de Bold AJ. Modulation of cardiac natriuretic peptide gene expression following endothelin type A receptor blockade in renovascular hypertension. *Cardiovasc Res* 2001;49:808-16.
- Kohse KP, Feifel K, Mayer-Wehrstein R. Differential regulation of brain and atrial natriuretic peptides in hemodialysis patients. *Clin Nephrol* 1993;40:83-90.
- Fishbane S, Natke E, Maesaka JK. Role of volume overload in dialysis-refractory hypertension. *Am J Kidney Dis* 1996;28:257-61.
- Eisenhauer T, Talartschik J, Scheler F. Detection of fluid overload by plasma concentration of human atrial natriuretic peptide (h-ANP) in patients with renal failure. *Klin Wochenschr* 1998;64 Suppl 6:68-72.
- Zoccali C, Mallamaci F, Benedetto FA, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 2001;12:1508-15.
- Mallamaci F, Zoccali C, Tripepi G, et al. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 2001;59:1559-66.
- Kato J, Kitamura K, Matsui E, et al. Plasma adrenomedullin and natriuretic peptides in patients with essential or malignant hypertension. *Hypertens Res* 1999;22:61-6.
- Takeda T, Kohno M. Brain natriuretic peptide in hypertension. *Hypertens Res* 1995;18:259-66.
- Nishikimi T, Yoshihara F, Morimoto A, et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996;28:22-30.
- Nishikimi T, Futo Y, Tamano K, et al. Plasma brain natriuretic peptide levels in chronic hemodialysis patients. *Am J Kidney Dis* 2001;37:195-203.
- Nishikimi T, Minami J, Tamano K, et al. Left ventricular mass relates to average systolic blood pressure, but not loss of circadian blood pressure in stable hemodialysis patients: an ambulatory 48-hour blood pressure study. *Hypertens Res* 2001;24:507-14.
- Franz M, Woloszczuk W, Hörl WH. N-terminal fragments of the proatrial natriuretic peptide in patients before and after hemodialysis treatment. *Kidney Int* 2000;58:374-83.
- Winters CJ, Vesely DL. Change in plasma immunoreactive N-terminus, C-terminus, and 4,000-dalton midportion of atrial natriuretic factor prohormone with hemodialysis. *Nephron* 1991;58:17-22.
- Franz M, Woloszczuk W, Hörl WH. Adsorption of natriuretic factors in uremia. *Semin Nephrol* 2001;21:298-302.
- Nishikimi T, Futo Y, Tamano K, et al. Plasma brain natriuretic peptide levels in chronic hemodialysis patients: influence of coronary artery disease. *Am J Kidney Dis* 2001;37:1201-8.
- Lee SW, Song JH, Kim GA, et al. Plasma brain natriuretic peptide concentration on assessment hydration status in hemodialysis patients. *Am J Kidney Dis* 2003;41:1257-66.
- Wallin CJB, Rossi P, Jacobsen SH, Leksell LG. Central blood volume, atrial natriuretic peptide and intermittent hemodialysis. *Scand J Urol Nephrol* 2004;38:78-84.
- Iwashima Y, Horio T, Takami Y, et al. Effects of creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis* 2002;40:974-82.
- Ikeda T, Matsuda K, Itoh H, et al. Plasma levels of brain and atrial natriuretic peptides elevate in proportion to left ventricular end-systolic wall stress in patients with aortic stenosis. *Am Heart J* 1997;133:307-14.
- Qi W, Mathisen P, Kjekshus J, et al. Natriuretic peptides in patients with aortic stenosis. *Am Heart J* 2001;142:725-32.
- Gerber IL, Stewart RAH, Legget ME, et al. Increased plasma natriuretic peptides reflect symptom onset in aortic stenosis. *Circulation* 2003;107:1884-90.
- Bergler-Klein J, Klar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;109:2302-8.
- Berger R, Huelsmann M, Strecker K, et al. Neurohormonal risk stratification for sudden death and death owing to progressive heart failure in chronic heart failure. *Eur J Clin Invest* 2005;35:24-31.
- Cataliotti A, Malatino LS, Jougasaki M, et al. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc* 2001;76:1111-9.
- Goto T, Takase H, Toriyama T, et al. Increased circulating levels of natriuretic peptides predict future cardiac event in patients with chronic hemodialysis. *Nephron* 2002;92:610-5.
- Ilebekk A, Christensens G, Leistad D, Rutlen D. Atrial natriuretic factor increases peritoneal fluid formation in the pig. *Acta Physiol Scand* 1993;149:121-2.
- Bianciotti L, Vatta M, Bengochea L, et al. Atrial natriuretic factor increases peritoneal efficiency in nephrectomized rats. *Peptides* 1996;17:87-92.
- Wang T, Cheng H-H, Heimbürger O, et al. Intraperitoneal atrial natriuretic peptide increases peritoneal fluid and solute removal. *Kidney Int* 2001;60:513-9.
- Pevahouse JB, Flanigan WJ, Winters CJ, Vesely DL. Normalization of elevated circulating N-terminal and C-terminal atrial natriuretic factor prohormone concentrations by renal transplantation. *Transplantation* 1992;53:1375-7.
- Raine AE, Anderson JV, Bloom SR, Morris PJ. Plasma atrial natriuretic factor and graft function in renal transplant recipients. *Transplantation* 1989;48:796-800.
- Sands JM, Neylan JF, Olson RA, et al. Atrial natriuretic factor does not improve the outcome of cadaveric renal transplantation. *J Am Soc Nephrol* 1991;1:1081-6.

35. Franz M, Woloszczuk W, Hörl WH. N-terminal fragments of the proatrial natriuretic peptide in plasma and urine of kidney graft recipients. *Transplantation* 2001;72:89–94
36. Shields PP, Dixon JE, Glembotski CC. The secretion of atrial natriuretic factor-(99–126) by cultured cardiac myocytes is regulated by glucocorticoids. *J Biol Chem* 1988;263:12619–28.
37. Day ML, Schwartz D, Wiegand RC, et al. Ventricular atriopeptin: unmasking of messenger RNA and peptide synthesis by hypertrophy or dexamethasone. *Hypertension* 1987;9:485–91.
38. Conger JD, Falk SA, Yuan BH, Schrier RW. Atrial natriuretic peptide and dopamine in a rat model of ischemic acute renal failure. *Kidney Int* 1989;35:1126–32.
39. Lieberthal W, Sheridan AM, Valeri CR. Protective effect of atrial natriuretic factor and mannitol following renal ischemia. *Am J Physiol Renal Fluid Electrolyte Physiol* 1990;258:F1266–72.
40. Marin-Grez M, Fleming JT, Steinhausen M. Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. *Nature* 1986;324:473–7.
41. Morrissey EC, Wilner KD, Barager RR, et al. Atrial natriuretic factor in renal failure and posthemodialytic postural hypotension. *Am J Kidney Dis* 1988;12:510–5.
42. Nakamoto M, Shapiro JL, Shanley PF, et al. In vitro and in vivo protective effect of atriopeptin III on ischemic acute renal failure. *J Clin Invest* 1987;80:698–705.
43. Neumayer HH, Blosser N, Seherr-Thohs U, Wagner K. Amelioration of postischemic acute renal failure in conscious dogs by human atrial natriuretic peptide. *Nephrol Dial Transplants* 1990;5:32–8.
44. Ortola FV, Ballermann BJ, Brenner BM. Endogenous ANP augments fractional excretion of Pi, Ca, and Na in rats with reduced renal mass. *Am J Physiol Renal Fluid Electrolyte Physiol* 1988;255:F1091–7.
45. Rahman SN, Kim GE, Mathew AS, et al. Effects of atrial natriuretic peptide in clinical acute renal failure. *Kidney Int* 1994;45:1731–8.
46. Schafferhans K, Heidbreder E, Grimm D, Heidland A. Norepinephrine-induced acute renal failure: beneficial effects of atrial natriuretic factor. *Nephron* 1986;44:240–4.
47. Shaw SG, Weidmann P, Hodler J, et al. Atrial natriuretic peptide protects against ischemic renal failure in the rat. *J Clin Invest* 1987;80:1232–7.
48. Meyer M, Pfarr E, Schirmer G, et al. Therapeutic use of the natriuretic peptide anaritide in acute renal failure. *Renal Fail* 1999;21:85–100.
49. Schramm L, Heidbreder E, Schaar J, et al. Toxic acute renal failure in the rat: effects of diltiazem and urodilatin on renal function. *Nephron* 1994;68:454–61.
50. Shaw SG, Weidmann P, Zimmermann A. Urodilatin, not nitroprusside, combined with dopamine reverses ischemic acute renal failure. *Kidney Int* 1992;42:1153–9.
51. Allgren RL, Marbury TC, Rahman SN, et al. Anaritide in acute tubular necrosis. *N Engl J Med* 1997;336:828–34.
52. Brenner RM, Chertow GM. The rise and fall of atrial natriuretic peptide for acute renal failure. *Curr Opin Nephrol Hypertens* 1997;6:474–6.
53. Martin DR, Pevahouse JB, Trigg DJ, et al. Three peptides from the ANF prohormone NH<sub>2</sub>-terminus are natriuretic and/or kaliuretic. *Am J Physiol* 1990;258:F1401–8.
54. Vesely DL, Douglass MA, Dietz JR, et al. Negative feedback of atrial natriuretic peptides. *J Endocrinol Metab* 1994;78:1128–34.
55. Vesely DL, Douglass MA, Dietz JR, et al. Three peptides from the atrial natriuretic factor prohormone amino terminus lower blood pressure and produce diuresis, natriuresis, and/or kaliuresis in humans. *Circulation* 1994;90:1129–40.
56. Nasser A, Dietz JR, Siddique M, et al. Effects of kaliuretic peptide on sodium and water excretion in persons with congestive heart failure. *Am J Cardiol* 2001;88:23–9.
57. Vesely DL, Dietz JR, Parks JR, et al. Comparison of vessel dilator and long acting natriuretic peptide in the treatment of congestive heart failure. *Am Heart J* 1999;138:625–32.
58. Vesely DL, Dietz JR, Parks JR, et al. Vessel dilator enhances sodium and water excretion and has beneficial hemodynamic effects in persons with congestive heart failure. *Circulation* 1998;98:323–9.
59. Clark LC, Farghaly H, Saba SR, Vesely DL. Amelioration with vessel dilator of acute tubular necrosis and renal failure established for 2 days. *Am J Physiol Heart Circ Physiol* 2000;278:H1555–64.
60. Vesely DL. Natriuretic peptides and acute renal failure. *Am J Physiol Renal Physiol* 2003;285:F167–77.
61. Mazul-Sunko B, Zarkovic N, Vrkic N, et al. Proatrial natriuretic peptide (1–98), but not cystatin C, is predictive for occurrence of acute renal insufficiency in critically ill septic patients. *Nephron Clin Pract* 2004;97:c103–7.