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Natriuretic peptide and adrenomedullin levels in chronic renal failure and effects of peritoneal dialysis

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Plasma levels of B-type natriuretic peptide (BNP) and its N-terminal propeptide (NT-BNP) are elevated in renal impairment and provide a robust prognostic index. The effect of peritoneal dialysis on plasma NT-BNP, however, is unknown. Furthermore, no information exists regarding levels of the N-terminal propeptide for C-type natriuretic peptide (NT-CNP) in renal failure and the effects of peritoneal dialysis. Accordingly, we documented venous levels of these peptides, and adrenomedullin, across peritoneal dialysis. We measured venous BNP, NT-BNP, NT-CNP, adrenomedullin, blood urea nitrogen (BUN) and creatinine before, during and after completion of overnight peritoneal dialysis in 11 patients, and identical sampling was carried out in eight patients (controls) but between peritoneal dialysis treatments. Peptide levels were measured using well-validated, published methods. Baseline levels of NT-CNP (212, 150–303 pmol/l, median and 25th and 75th percentiles) were much higher than recorded previously in healthy volunteers or in heart failure, and correlated with plasma creatinine ($r_s = 0.53$, $P < 0.05$). Peritoneal dialysis had no effect on plasma NT-CNP, nor on NT-BNP, BNP or adrenomedullin (all elevated above normal), whereas both BUN and creatinine levels, as expected, declined ($P < 0.001$). We conclude that plasma levels of NT-CNP are grossly elevated in chronic renal failure and correlated with plasma creatinine, but are not altered by peritoneal dialysis. Likewise, BNP, NT-BNP and adrenomedullin are elevated but are not altered by peritoneal dialysis. This information is needed if levels of these hormones are to be used as prognostic indicators or as a guide to the management of patients with chronic renal failure.

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It is known that circulating concentrations of the bioactive cardiac natriuretic peptides, atrial and B-type natriuretic peptide (A-type peptide (ANP) and B-type peptide (BNP), respectively), are elevated in patients with impaired renal function.[1,2] Most reports are that plasma levels of these peptides relate not only to the severity of renal dysfunction but also to indices of cardiac structure and function such as left ventricular ejection fraction (inverse correlation) and left ventricular diameters, left ventricular mass index, and pulmonary artery or wedge pressure (positive correlations).[2,3] Furthermore, the CREED investigators, who studied a large cohort of patients requiring chronic dialysis, showed that plasma BNP and ANP levels were robust predictors of total and cardiovascular mortality.[4] Accordingly, it is possible that circulating concentrations of these peptides will provide an objective guide for the management of such patients in regard to their dietary habits, dialysis requirements and pharmacological treatment.[5]

Interpretation of plasma cardiac natriuretic peptide levels in patients with chronic renal failure, however, requires an understanding of the effects of dialysis on their circulating concentrations. Hemodialysis- and peritoneal dialysis-induced effects on plasma ANP and BNP have been reported, but it is not known whether levels of the 1–76 amino-acid N-terminal fragment (NT-BNP) of proBNP are altered by peritoneal dialysis. This is of potential importance as there has been speculation that NT-BNP might provide a better index of cardiac function or dysfunction than BNP itself.[6]

The first aim in the present study, therefore, was to document NT-BNP levels across peritoneal dialysis. The second aim was to record plasma levels of peptides that are likely to afford cardiovascular protection in patients with chronic renal failure and the effects on them of peritoneal dialysis. One is the recently discovered N-terminal fragment (NT-C-type natriuretic peptide (CNP)) of the propeptide of the third natriuretic peptide, CNP,[7] which circulates at higher concentrations than CNP itself. The other peptide is adrenomedullin, which is secreted largely by the vascular endothelium and whose levels are known to be elevated in renal failure.[8]

RESULTS

Characteristics of patients in the active and control groups are shown in Table 1. Body weight declined across dialysis by an average of 2.2 kg in the active group (range 0–5 kg). Plasma levels of BNP, NT-BNP, NT-CNP and adrenomedullin were elevated well above the normal range as determined in healthy volunteers using the same radioimmunoassays (Table 1). In the case of NT-CNP, the levels (212, 150–303 pmol/l, median and 25th and 75th percentiles) were also very much higher ($P<0.001$) than documented previously in 77 patients aged 74 ± 1.8 years (mean $\pm$ s.e.m.) with heart failure (32.4, 25.4–39.4 pmol/l)[9] and 101 healthy volunteers aged 66.5 ± 0.8 years (18.5, 15.8–28.9 pmol/l), again using the same assay (Figure 1). Baseline indices were similar in the two groups of patients with chronic renal failure except for plasma levels of NT-CNP, which were significantly higher in the active group than in controls ($P<0.01$).

Table 1 | Baseline indices (mean $\pm$ s.e.m., or median and interquartile range) in patients with chronic renal failure

	Active group (n=11)	Control group (n=8)	Normal range
Age (years)	44.7 $\pm$ 8	45.1 $\pm$ 5	—
Weight (kg)	67.5 $\pm$ 6	67.4 $\pm$ 4	—
Plasma BUN (mg/dl)	80 (59, 115)	92 (77, 114)	5–25
Plasma creatinine (mg/dl)	10.0 (6.6, 15.3)	7.4 (4.9, 11.3)	0.5–1.5
Plasma BNP (pmol/l	13.5 (8.0, 49.7)	14.1 (5.5, 149.6)	3–12
Plasma NT-BNP (pmol/l)	54 (41, 678)	81 (27, 1500)	2–50
Plasma NT-CNP (pmol/l)	269 (212, 321)**	148 (93, 167)	13–29
Plasma adrenomedullin (pmol/l)	9.5 (7.9, 18.7)	9.6 (7.6, 32.7)	4–28

**$P<0.01$ compared to the control group.

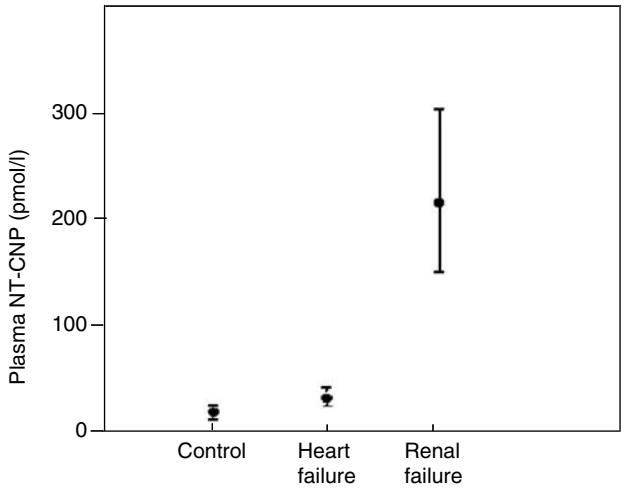

Figure 1 | Plasma levels of NT-CNP in healthy volunteers ($n=101$), patients with heart failure ($n=77$) and patients with chronic renal failure ($n=19$). Data are shown as median and 25th and 75th percentiles.

A statistically significant association was noted between baseline plasma levels of NT-CNP and creatinine ($r_s=0.53$, $P<0.05$, $n=19$, Figure 2). Patient age was not significantly related to any of the peptide hormones but correlated inversely with baseline levels of plasma creatinine ($r_s=-0.46$, $P<0.05$).

Plasma blood urea nitrogen (BUN) and creatinine levels fell significantly ($P<0.001$) across dialysis compared to those of controls (−25 (−36, −4) versus 2 (0.4, 4) mg/dl and −1.2 (−2.7, −0.5) versus 0.0 (−0.2, 0.4) mg/dl). By contrast, plasma levels of BNP, NT-BNP, NT-CNP and adrenomedullin did not change in either active or control patients (Table 2).

DISCUSSION

It is clear from previous reports that plasma levels of cardiac natriuretic peptides are elevated in patients with chronic renal failure.[1,2] In that their levels in the plasma correlate with haemodynamic indices and left ventricular mass and also predict cardiovascular and total mortality,[2–4] there is every possibility that they might prove to be clinically useful as one index of cardiac dysfunction and fluid status, and as a guide to the complex management of patients requiring long-term dialysis.[5] Interpretation of natriuretic peptide levels, however, requires an understanding of what factors can alter their circulating concentrations. In this regard, it is known that plasma levels of ANP fall substantially across both haemodialysis and peritoneal dialysis.[1,10] Compared with ANP, plasma BNP levels exhibit no change or a lesser percentage decline,[1,11] and Wahl *et al.*[12] reported that NT-BNP levels were altered little by haemodialysis, falling slightly (by 2.3%) when a high-flux membrane was used and

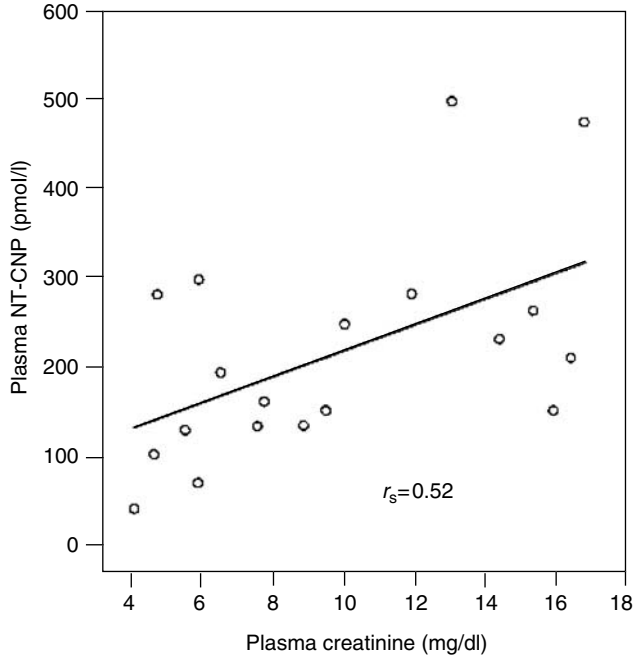

Figure 2 | Plasma levels of creatinine and NT-CNP in 19 patients with chronic renal failure.