

# Predialysis NTproBNP Predicts Magnitude of Extracellular Volume Overload in Haemodialysis Patients

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## Key Words

NT-proBNP · Bioimpedance · Extracellular fluid volume · Haemodialysis

## Abstract

**Introduction:** Increased natriuretic peptides are associated with increased cardiovascular and all-cause mortality for haemodialysis (HD) patients. However, debate continues whether these biomarkers are increased by extracellular water (ECW) excess and can be used to aid clinical assessment of volume status and help determine target weight. **Methods:** We measured N terminal probrain natriuretic peptide (NT-proBNP) predialysis in 375 stable haemodialysis outpatients with corresponding pre and postdialysis multifrequency bioelectrical impedance assessments (MFBIA) of (ECW)/total body water (TBW). **Results:** Median age 64 (51–75), 63.9% male, 42.9% diabetic, 43.2% Caucosoid, 14.4% with a history of myocardial infarction, 8.4% coronary artery bypass surgery, dialysis vintage 28.2 (12.3–55.5) months. Median predialysis NT-proBNP 283 (123–989) pmol/l, and predialysis ECW/TBW ratio  $0.397 \pm 0.029$ . On multivariate analysis, predialysis log NT-proBNP was associated with predialysis systolic blood pressure ( $\beta$  0.007,  $p = 0.000$ ), weight ( $\beta$   $-0.008$ ,  $p = 0.001$ ), valvular heart disease ( $\beta$  0.342,  $p = 0.015$ ), ECW/TBW ( $\beta$  1.3,  $p = 0.019$ ) and log CRP ( $\beta$  0.145,  $p = 0.037$ ).

Dividing patients into NTproBNP quartiles, %ECW/TBW and relative ECW overhydration were significantly greater for the highest quartile vs. lowest ( $40.5 \pm 4.1$  vs.  $39.0 \pm 1.1$ , and  $1.51 \pm 1.24$  vs.  $0.61 \pm 0.69$  l, respectively,  $p < 0.001$ ). **Conclusion:** In this study, predialysis NTproBNP values were associated with direct assessments of the extracellular volume excess measured by MFBIA and systolic arterial blood pressure. This suggests that predialysis NTproBNP values can potentially be used to aid clinical assessment of volume status in dialysis patients to determine target weight.

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## Introduction

Cardiovascular disease remains the most common cause of death in haemodialysis patients [1]. However, compared to the general population, haemodialysis patients have increased arteriosclerosis and left-ventricular hypertrophy, rather than atheromatous vascular disease. Similarly, haemodialysis patients have an increased prevalence of left-ventricular diastolic dysfunction, which may develop following recurrent episodes of volume overload predialysis [2]. Reducing the number of episodes of volume overload by more frequent dialysis was recently reported to lead to a reduction in both systolic

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blood pressure and left-ventricular mass [3]. Natriuretic peptides were introduced into routine general medical clinical practice as biomarkers to aid the diagnosis of heart failure. Previous studies have reported a strong inverse association between BNP and survival in dialysis patients [4]. Although BNP is filtered by the glomerulus and degraded in the proximal renal tubules, there is significant extra renal clearance of natriuretic peptides so that many dialysis patients can have normal concentrations [5]. As such there has been debate in the published literature as to whether measurement of natriuretic peptides can add value in aiding clinical judgement of volume status in haemo and peritoneal dialysis patients [6–12]. While NT-proBNP is not affected by peritoneal dialysis exchanges, NT-proBNP concentrations fall after high-flux haemodialysis and haemodiafiltration [13]. We therefore elected to determine whether predialysis NT-proBNP measurements were increased in patients with an expanded extracellular water space as measured by multifrequency bioelectrical impedance [13].

## Methods and Patients

375 stable established haemodialysis outpatients, attending their routine mid-week haemodialysis session, using either Fresenius 4008H/5000H or BBraun Dialogue+<sup>®</sup> dialysis machines with integrated blood pressure monitors (Fresenius Bad Homburg, Germany and BBraun, Melsungen, Germany), polysulfone dialyzers (Nipro Corporation, Osaka, Japan) [14], with ultrapure quality dialysis water and anticoagulation with low molecular weight heparin (Tinzaparin, Leo Laboratories, Princes Risborough, UK) [15] were studied. Multifrequency bio-electrical impedance assessments (MF-BIA) were standardized by taking measurements pre and 20–30 minutes postdialysis session, using an eight-electrode MF-BIA device (Biospace In body 720, Seoul, South Korea) [16, 17]. Patients with pacemakers or implantable defibrillators and amputees were excluded from study. Relative extracellular water volume (ECW) excess termed extracellular water overhydration was estimated according to the method recommended by the European Society for Parenteral and Enteral Nutrition (ESPN) [18].

Serum biochemistry samples were analysed with a standard multi-channel biochemical analyzer (Roche Integra, Roche diagnostics, Lewes, UK), using the bromocresol green method for albumin determination, NT-proBNP was measured by immunoassay (ECLIA Roche Diagnostics, GMBH, Mannheim, Germany), with an inter assay coefficient of variation 1.3%.

Electronic patient medical records were reviewed to obtain relevant clinical information and prescribed medication history.

Ethical approval was granted by the Royal Free Hospital research and development department as audit and clinical service development, and the audit was conducted according to the UK National Health Service guidelines on clinical audit and service development.

## Statistical Analysis

Results are expressed as mean  $\pm$  standard deviation, or median and interquartile range, or percentage. Statistical analysis was by Students' paired *t* test for parametric and the Wilcoxon rank sum pair test for nonparametric data, with Bonferroni correction for multiple analyses where appropriate, and anova with Tukey or Dunnett's post hoc correction (GraphPad Prism version 6.0, GraphPad, San Diego, Calif., USA). Simple correlation analysis was performed with Pearson's rank correlation and then multiple linear regression analysis using backward step multivariate analysis was used excluding variables that were not significant and did not improve the fit of the model, and retaining variables in the model where the 95% confidence intervals for the estimate did not include zero or there was an improvement in model fit (as demonstrated by the  $-2\log$  likelihood), using SPSS version 21.0 (SPSS, Univ Chicago, Ill., USA), which was also used to calculate a receiver operating characteristic curve (ROC) sensitivity and specificity analysis. Nonparametric variables were log transformed to allow analysis. Statistical significance was taken at or below the 5% level.

## Results

The median age of the 375 patients was 64 (51–75) years, 63.9% male, 42.9% diabetic, 43.2% Caucasoid, 38% African or Afro-Caribbean, 21.6% South Asian, with a dialysis vintage of 28.2 (12.3–65.5) months, and postdialysis body mass index of  $26.4 \pm 6.3$  kg/m<sup>2</sup>. Antihypertensive medications were prescribed to 51.1% of the patient cohort, with the average number of antihypertensive medications prescribed per patient 1 (0–1). The commonest antihypertensive medications prescribed were beta blockers 33.2%, followed by calcium channel antagonists at 12.8 and 10.5% for both angiotensin converting enzyme inhibitors and sartanes. 56.2% were prescribed aspirin or clopidogrel and 4.8% warfarin. 14.4% had a prior documented myocardial infarction, 8.4% coronary artery bypass surgery, 10.4% coronary artery stenting, 8.0% had heart valve replacement or severe valvular heart disease, 10.3% peripheral vascular disease, and 12.4% cerebrovascular disease mean dialysis session time 4 (3.5–4.0) hours, urea reduction ratio  $74.6 \pm 8.3\%$ . Predialysis haemoglobin  $113.4 \pm 13.9$  g/l, serum albumin 40 (37–42) g/l, blood glucose 6.4 (5.5–7.8) mmol/l, C-reactive protein 9.4 (2–11) mg/l. Pre and postdialysis biochemistries, blood pressure and bio-impedance assessments are set out in table 1.

NT-proBNP values were not normally distributed with the median predialysis NT-proBNP 283 (123–989) pmol/l. As such NTproBNP values were log transformed and were correlated with markers of volume overload; extracellular water to total body water ratio (ECW/TBW)

**Table 1.** Pre and postdialysis biochemistries, blood pressure and volume assessments

	Predialysis	Postdialysis
Serum urea, mmol/l	18.4±5.3	4.9±2.5***
Serum sodium, mmol/l	138.9±3.3	138.8±2.9
Systolic blood pressure, mm Hg	141.5±26.0	129.5±26.0***
Diastolic blood pressure, mm Hg	75.3±16.4	71.2±15.4**
Mean arterial blood pressure, mm Hg	97.0±17.0	90.2±17.6***
Intracellular water (ICW), l	22.7±5.9	21.5±4.1***
Extracellular water (ECW), l	14.9±3.9	13.4±2.8***
% Extracellular water/total body water	39.7±2.9	39.0±1.7***
Weight, kg	73.6±19.0	71.8±19.3***

Variables expressed as mean ± SD. \*\*\* p < 0.001 vs. predialysis.

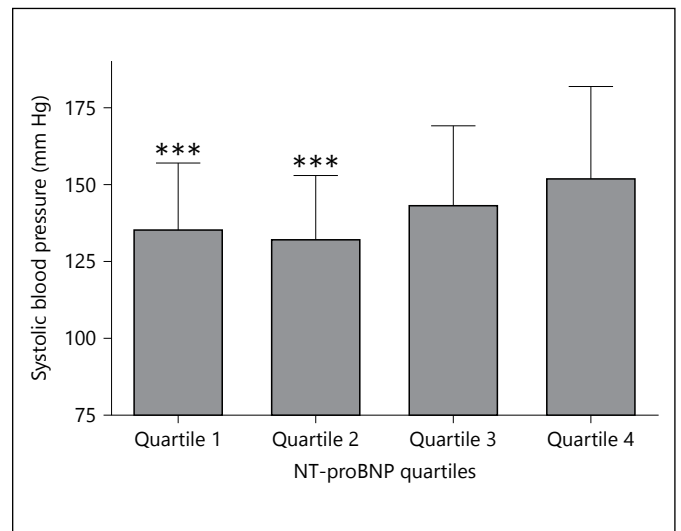
**Table 2.** Multiple regression model for logNTproBNP taken in the predialysis session

variable	β coefficient	SE	t	F	95% CL	p value
SBP, mm Hg	0.007	0.002	4.16	17.3	0.004 to 0.10	0.000
Weight, kg	-0.008	0.002	-3.5	12.24	-0.013 to -0.004	0.001
Valve	0.342	0.14	2.45	5.99	0.066 to 0.613	0.015
%ECW/TBW	0.013	0.03	2.36	5.56	0.005 to 0.056	0.019
log CRP, g/l	0.145	0.069	2.10	4.4	0.009 to 0.281	0.037

%ECW/TBW = Percentage extracellular weight/total body water ratio; SBP = systolic blood pressure; v = valvular heart disease; CRP = C-reactive protein; SE = standard error; CL = confidence limits and adjusted r<sup>2</sup> value for model 0.38.

relative extracellular water overhydration, age, sex, weight cardiovascular disease and also systolic blood pressure (online suppl. table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000368376](http://www.karger.com/doi/10.1159/000368376)). We then performed a backward multivariate analysis, excluding variables that were not significant or failed to improve the model fit and log predialysis NTproBNP was associated with ECW/TBW, valvular heart disease, C-reactive protein (CRP), systolic blood pressure, and weight (table 2).

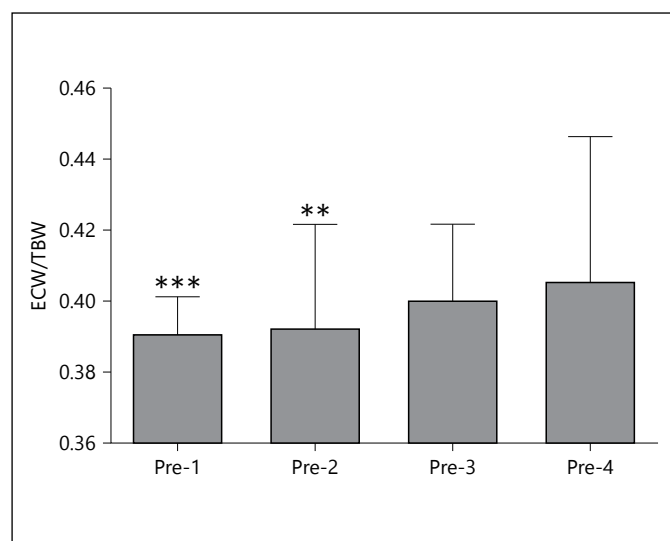
We then divided patients into quartiles of predialysis NTproBNP. Those patients in the highest NTproBNP had greater systolic blood pressure, both pre and postdialysis (fig. 1). Patients in the lowest NTproBNP were heavier, with greater body fat and had higher serum albumin and lower CRP concentrations (table 3). Although bioimpedance assessments did not show absolute differences (table 3), both relative extracellular water overhydration and the ratio of extracellular water (ECW) to total body water (TBW) were greater in those in the highest quartile cohort both pre and postdialysis (fig. 2 and 3).

**Fig. 1.** Systolic blood pressure (mm Hg) pre dialysis in patients divided into four quartiles according to predialysis NT-proBNP pmol/l. Values expressed as mean ± SD. \*\* p < 0.01 and \*\*\* p < 0.001 vs. 4th quartile (highest NTproBNP group).

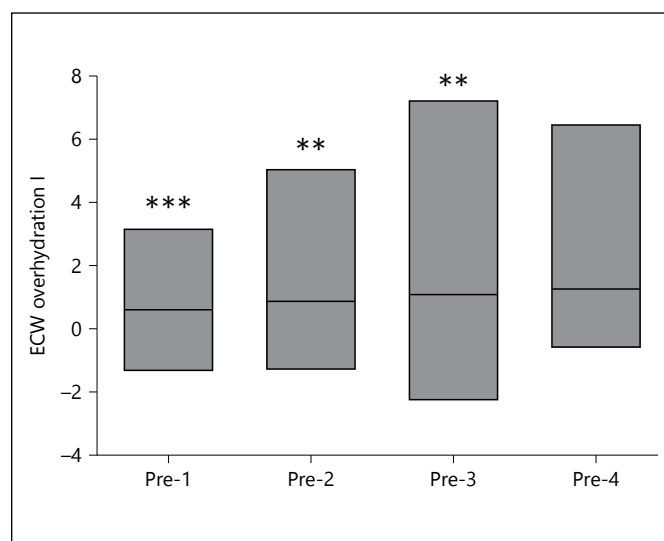
**Table 3.** Patients divided into predialysis NTproBNP quartiles. Patients prescribed antihypertensive medications (BP meds) and patients prescribed 2 or more different antihypertensive agents ( $\geq 2$  BP meds)

NTproBNP, pmol/l	<123	123–283	283–989	>989
Age, years	57.1±16	61.7±16.7	65.3±14.1	64.6±16.2
Male, %	63.8	70.0	64.1	60.9
Caucasoid, %	31.9*	49.4	43.4	50.5
Diabetic, %	42.6	35.4	47.8	46.3
Vintage, months	22.2 (12–58)	27.3 (13–63)	28.7 (12–67)	43 (11–71)
BP meds, %	41.3*	45.8	56.4	61.3
$\geq 2$ BP meds	16.0*	16.7*	16.5*	32.3
MI, %	5.3*	4.2*	17.4	20.4
valve disease, %	3.3*	4.2*	8.7	17.2
Weight, kg	79.7±19.9*	75.6±20.6*	71.7±17.5	66.9±15.4
ICW, l	24.1±5.7	23.5±7.0	21.5±5.0	21.8±5.5
ECW, l	15.4±3.5	15.2±4.8	14.3±3.2	15.9±4.3
% body fat	31.8±12.0*	30.1±11.4	31.3±11.7	25.0±13.4
MAP pre, mm Hg	95.1±14.3*	92.0±14.1*	97.3±15.7	103.9±21.0
MAP post, mm Hg	88.7±14.9*	86.2±15.4*	91.4±14.3	95.8±21.4
Haemoglobin, g/l	117±13	112±14	113±14	112±17
Albumin, g/l	40.7±5.0	39.9±3.7	38.8±3.1	38.6±3.9
CRP, g/l	3 (1–8)*	5 (2–11)*	5 (2–10)	7 (3–16)
URR, %	73.7±8.7	76.0±6.5	74.8±8.7	73.4±8.6

MI = Past medical history myocardial infarction; v = valvular heart disease; ICW = predialysis weight and bioimpedance volume assessments, intracellular water; ECW = extracellular water; MAP = mean arterial blood pressure; CRP = C-reactive protein; URR = urea reduction ratio. Data expressed as mean  $\pm$  standard deviation or median (interquartile range) or percentage. \*  $p < 0.05$  vs. highest NTproBNP quartile after correcting for multiple testing.



**Fig. 2.** Extracellular water (ECW) to total body water (TBW) ratio pre dialysis in patients divided into four quartiles according to predialysis NT-proBNP pmol/l. Data expressed as mean  $\pm$  SD. \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  vs. 4th quartile (highest NTproBNP group).



**Fig. 3.** Relative extracellular water (ECW) overhydration according to ESPEN guidelines pre dialysis, in patients divided into four quartiles according to predialysis NT-proBNP pmol/l. Data expressed as median, interquartile range and minimum to maximum. \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  vs. 4th quartile (highest NTproBNP group).

Fluid overload in a haemodialysis patient is not simply present or absent, but rather a gradation. We therefore took a pragmatic approach to defining overhydration by using an ECW/TBW ratio of  $\geq 0.415$ , which was 2 standard deviations from the postdialysis values and  $\geq 2.0$  litre ECW excess, as defined by the ESPEN [18]. The relative area under ROC curves for predialysis NTproBNP for an ECW/TBW ratio of  $\geq 0.415$  and ECW excess of 2.0 were 0.79 (95% confidence limits 0.72–0.85) and 0.73 (0.65–0.8), respectively.

## Discussion

Although previous reports of BNP measurements in dialysis patients have concurred that BNP is a strong prognostic marker for cardiac and all-cause mortality [4], there is debate as to whether BNP has any value in helping to determine volume status in dialysis patients [10, 19]. In part, this is due to the lack of standardization of the different commercial and locally developed assays for natriuretic peptides, which are now available. Although BNP and NT-proBNP are co-secreted in equimolar amounts from the left and right cardiac ventricles in response to ventricular volume expansion and pressure overload, the larger NTproBNP, has a longer half-life, and is much more stable than BNP [20, 21]. BNP values are more variable due to the shorter biological half-life of 10–20 min, but also because BNP is less stable in vitro, especially if blood is not collected into plastic tubes containing EDTA, or without other agents designed to prevent degradation and also if analysis is delayed [22, 23]. Predialysis BNP values vary with the dialysis week, being highest when patients are most volume overloaded prior to the first dialysis session of the week and lowest before the third dialysis session [24]. In addition, while there is little or no clearance with low flux dialysis, some clearance occurs with both high-flux dialysis and haemodiafiltration, although the difference postdialysis is least after the last dialysis session of the week [24]. As such, we chose to standardise the results by making measurements prior to the mid-week dialysis session. In keeping with previous reports, we found that NTproBNP was increased in patients with a history of previous heart disease, including valvular heart disease, myocardial infarction, coronary artery bypass surgery and stenting and the number of antihypertensive drugs prescribed [4, 9]. The general population-based Framington study, and other studies in haemodialysis patients [11] have reported that overweight patients, and those with a greater body mass

index had lower NTproBNP concentrations [25]. Our results are in agreement with these findings, but while reports in the general population have linked obesity to lower BNP values [26], we observed greater NTproBNP values in those with lower body fat. This may reflect differences in body composition associated with chronic uraemia and dialysis compared to the healthy general population [17, 27].

Although some reports have suggested that BNP does not reflect volume status [10], we found that NTproBNP was greater in those patients with higher systolic blood pressure both pre and postdialysis, and although there was a simple correlation between NTproBNP and systolic blood pressure, the *r* value was only 0.303, and as such, systolic blood pressure accounted only for some 9% of the variance in NTproBNP in our study population. According to the bioimpedance studies, most of the ECW gain between dialysis sessions is in the legs and trunk. As ECW gain does not directly equate with plasma volume expansion, there is a limited association with systolic blood pressure.

We observed an increased ECW to TBW ratio both pre and postdialysis and NTproBNP, linking NTproBNP to volume overload. In addition, we also expressed ECW excess as relative overhydration as suggested by the ESPEN [18], and again patients with the highest NTproBNP concentrations had greater ECW over-hydration both pre and postdialysis. Although our results support several previous studies [4, 7, 8, 12], the ratio of ECW/TBW can be increased by both expansion of the ECW and reduction in TBW because of a loss of intracellular water [8]. As such, this may link inflammation and malnutrition with volume overload [8, 27–29] due to increased vascular permeability. To support this relationship, we observed univariate associations for serum CRP and inverse correlations with serum albumin, haemoglobin and body cell mass. However, on multivariate analysis only CRP remained statistically significant.

We also found that the quartile with the highest NTproBNP concentrations had lower postdialysis weights and although similar dialysis session urea reduction ratios, received shorter dialysis session times. This may suggest that smaller patients receive shorter dialysis session times [30, 31], and as such may fail to achieve their target weight as unable to tolerate fluid removal in a shorter period [32]. This would support data that patients of normal body mass index (BMI) and women are reported to have reduced survival on haemodialysis in the United States because they typically have shorter session times compared to men and those with higher BMIs [29, 33].

Our results show that predialysis NTproBNP is increased with extracellular volume overload in haemodialysis patients and as such could potentially be used as a guide to aid clinical judgement in determining the target weight. There is some clearance of NTproBNP with high-flux haemodialysis and haemodiafiltration, but as NTproBNP is one of the larger BNP peptides, clearance is much lower than with other BNP peptides. Previous studies have measured postdialysis NTproBNP; however, the area under the ROC curve was somewhat lower 0.72, and the 95% confidence limit range was wider at 0.58–0.86 [11]. As such, predialysis estimations of NTproBNP appear to have greater clinical relevance in helping to assess volume status in dialysis patients. Serial estimations of BNP peptides [19] are more likely to be helpful in monitoring changes in target weight than single-point measurements. Although multi-frequency bioelectrical impedance assessments are an accepted method for assessing volume status in dialysis patients, this technique cannot be used for all patients, particularly those with implantable defibrillators and some car-

diac pace makers, and amputees. In addition, total body bioimpedance devices may provide inaccurate estimations of hydration status in haemodialysis patients with unilateral limb swelling or superior vena cava obstruction [33]. As such, there may be a role for measuring natriuretic peptides. Although both pre and post NTproBNP measurements appear to be of similar predictive value, it would be more useful to measure NTproBNP prior to dialysis to aid clinical assessment of volume status, especially as point-of-care testing now allows for bedside monitoring.

### Disclosure Statements

The authors have no conflicts of interest. The data presented has not been previously published in whole or part form.

### Source of Funding

Royal Free Hospital.

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