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Original Article

Volume Control

Brain natriuretic peptide reflects individual variation in hydration status in hemodialysis patients

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Abstract

Introduction: Fluid management in hemodialysis patients is a controversial topic. Brain natriuretic peptide (BNP) is secreted from the heart in response to volume overload, and may be a marker of overhydration in hemodialysis patients. Our aim was to investigate the correlation between BNP and overhydration in a cohort of hemodialysis patients, and to find out whether BNP and overhydration correlate in repeated measurements within individuals with elevated BNP.

Methods: The study was prospective, observational, and had a cross-sectional part and a longitudinal follow-up. The distribution of BNP was investigated in a cohort of 64 hemodialysis patients. Blood samples and bioimpedance spectroscopy measurements were performed before midweek dialysis. Subsequently, 11 study participants with elevated BNP concentrations (>500 pg/mL) were assessed in another nine dialysis sessions each. These individuals also had their cardiac function and heart rate variability (HRV) examined.

Findings: BNP was above 500 pg/mL in 38% of the participants, and correlated positively with overhydration (r_s = 0.381), inflammation and malnutrition, but not with systolic blood pressure. In comparison to participants with BNP below 500 pg/mL, participants with elevated BNP were older, had lower muscle strength, lower bodyweight and lower levels of hemoglobin and albumin. Echocardiography revealed cardiac anomalies in all 11 participants in the longitudinal follow-up, and HRV, as measured by SDNN, was pathologically low. In repeated measurements, the between-individuals variation of BNP in relation to overhydration was greater (SD = 0.581) than the within-person variation (SD = 0.285).

Discussion: BNP correlates positively to overhydration, malnutrition, and inflammation. In a subgroup of patients with elevated BNP, who are mainly elderly and frail, BNP reflects individual variation in hydration status, and hence seems to be a modifiable marker of overhydration. These data suggest that BNP is best applied for measuring changes in hydration status within an individual over time.

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INTRODUCTION

Chronic overhydration has been identified as an independent predictor of mortality in hemodialysis patients.[1–3] Overhydration is associated with inflammation,[4] left ventricular hypertrophy, left ventricular dilation, arterial hypertension, and the eventual development of congestive heart failure.[5,6] More than 25% of all hemodialysis patients are overhydrated, while a large proportion have a fluid deficit.[7] Thus, volume control is insufficient and more objective and reliable methods for assessment of hydration status need to be developed.

An increasingly common method for assessing hydration status is bioimpedance spectroscopy, which is a noninvasive method for measuring extracellular volume and total body water.[8,9] Fluid management based on bioimpedance measurements may help to improve blood pressure control, overall overhydration, and arterial stiffness.[10–13] However, bioimpedance analysis does not differentiate between intravascular and interstitial water content,[14,15] and normalization of hydration status in hemodialysis patients may for instance lead to a decrease in residual renal function.[10] Hence, a supplemental independent measurement of intravascular water content would be beneficial.[16,17]

Brain natriuretic peptide (BNP) plays a major role in salt and water homeostasis, protecting the cardiovascular system from the effects of volume overload. It is a polypeptide secreted by the cardiomyocytes in response to stresses such as excessive stretching and hypoxia.[18,19] BNP derives from preproBNP, which is transformed into proBNP and then split into BNP and the biologically inactive NT-proBNP, which are each secreted in equal amounts. Both BNP and NT-proBNP can be used for screening and prognosis in heart failure.[20,21] Elevated levels are also observed in pulmonary hypertension.[22]

In theory, BNP should be a good indicator of overhydration, since it is secreted from the heart in response to volume overload. However, using BNP as a marker of overhydration in dialysis patients is controversial,[23–27] as not only hydration status but a number of other factors, such as a patient's degree of heart failure, hemodialysis treatment modalities, and adverse events during dialysis affect BNP levels.[28] Elevated BNP levels seem to indicate overhydration, but do not give information about normohydration or underhydration.[29] After calculating the area under the receiver operating characteristic curve in order to try and find the best cutoff threshold values of BNP for overhydration, Lee and Tapolyai[29,30] have suggested a value of 500 pg/mL to differentiate between hemodialysis patients with or without volume overload. BNP concentrations have been found to vary considerably across the dialysis population, but when BNP is already elevated (due to biological variation or pathophysiological processes), fluctuations in hydration status presumably account for some of the variance.[16,31,32]

In this prospective study the correlation between BNP, overhydration and inflammation was investigated. The study was designed to explore the distribution of BNP, in a cohort of hemodialysis patients, in order to identify individuals with elevated BNP concentrations. The aim was to compare the variation of correlation between BNP and overhydration within-subjects to variation of correlation between subjects in repeated measurements, in hemodialysis patients with elevated BNP.

MATERIALS AND METHODS

Design and sample

The study was prospective, observational, single center, and consisted of a cross-sectional part and a longitudinal follow-up. Ethical approval was obtained from the Regional Ethical Review Board in Uppsala, Sweden (Reg. No. 2017/006). The study complied with the Declaration of Helsinki, and written informed consent was obtained from all study participants.

The study sample of the cross-sectional part was based on an entire cohort of patients of a Swedish hemodialysis center (n = 81). Criteria for inclusion were treatment with intermittent hemodialysis for ≥3 months, age ≥18 and ability to give informed consent. Criterion for exclusion was having single-pooled pacemaker implant, since this is incompatible with the use of bioimpedance measurement.

Participants with elevated BNP levels (>500 pg/mL)[29,30] were assessed on nine additional visits—on three consecutive sessions of three separate study weeks, with 1–3 weeks between each study week. As dialysis modalities may affect BNP concentrations[28] these patients were transferred to treatment with high permeable dialyzers, and individuals on dialysis treatment deviating from thrice weekly were excluded. Because cardiac autonomic function may be compromised in hemodialysis patients,[33] and there is an association between impaired heart rate variability (HRV), overhydration and

cardiovascular outcome[34,35] cardiac function was examined by both echocardiography (ECG) and HRV.

Data collection

Collection of blood samples, blood pressure measurements and bioimpedance measurements were performed predialysis. Cross-sectional data were collected prior to one midweek dialysis session between March and June 2017. The first observation point of the longitudinal follow-up was performed after a median time of 26 (23–31) weeks after baseline.

BNP assays were performed using an Alere Triage Meter-Pro (Alere Inc., DE, USA). This device was chosen as it returns measurement within 15 minutes, enabling bedside assessment. NT-proBNP has a half-life of 2 hours while BNP has a half-life of 18 minutes. We chose to investigate BNP rather than NT-proBNP as a marker of overhydration because BNP levels in dialysis patients differ less from non-dialysis subjects,[36] and are less affected by dialysis treatment modalities than are NT-proBNP levels.[22,28,37]

Hydration status was measured by bioimpedance spectroscopy using the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany). The instrument analyzes the resistance and reactance of human tissue, and returns measurements on absolute overhydration (AOH) in liters (L), and relative overhydration (ROH, %), which is the ratio of AOH volume to the extracellular fluid water.[8,9,38] Two single values exceeding −20% overhydration were considered implausible and possible artifacts, and as such excluded from further analysis. In order to clinically assess the hydration status, a quantitative score of volume state, originally published by Wizemann and Schilling[39] and later modified and described by Kraemer et al.,[40] was used. Blood pressure and heart rate were measured with the blood pressure monitor integrated in a Fresenius 5008 hemodialysis machine (Fresenius Medical Care, Bad Homburg, Germany).

Information about medical history, treatment modalities, additional biomarkers and nutritional status was collected from the medical records. Small-solute clearance is currently considered the best measure of hemodialysis adequacy.[41] An expression of clearance that includes the patient's treatment time (t) and adjustment for patient size is Kt/V. To adjust for hemodialysis schedules other than thrice weekly a method of calculation that includes the contribution of ultrafiltration, standard Kt/V (stdKt/V) was used in this study. Although, in the absence of data on residual renal function, the equation gives a value for StdKt/V that is ∼7% higher.[41] For analysis of inflammatory markers, blood was collected in Ethylenediaminetetraacetic acid (EDTA) tubes and plasma-separated within 5 hours of collection. Plasma was stored at −70°C until assayed. Human cathepsin L, cathepsin S, endostatin, galectin-9, IL1-beta, IL6, IL10, MMP-9, neprilysin, TNF-alpha, sTNF RI/TNFRSF1A, and sTNF RII/TNFRSF1B were analyzed by commercial sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA), and the absorbance was measured in a SpectraMax 250 (Molecular Devices, Sunnyvale, CA, USA). Values of inflammatory markers exceeding reference intervals of analysis device were coded as follows: IL6 < 10 transformed to 5, IL1 Beta < 2 to 1, neprilysin >12,000 to 12,100, IL 10 < 15 to 7.5 and > 3000 to 3010. Also C-reactive protein (CRP) was used as a marker of inflammation.

HRV was measured once between two dialysis sessions with 24–48 h Holter electrocardiography, using SEER light recorder (GE Medical Systems). All HRV recordings were analyzed using multiparameter analysis and review system (MARS) version 6.0 on a MARS PC workstation (GE Medical Systems, Chicago, Illinois, USA), and time domain analyses of beat-to-beat interval (RR) variability were calculated. Frequency domain measures of RR variability were assessed with power spectral analysis of 5-minute ECG-recordings by a nonparametric (fast Fourier transformation) method.

Statistical analysis

Statistical analyses were performed using version 25.0 of IBM SPSS Statistics for Macintosh (IBM, Armonk, NY, USA). R version 3.3.2 was used for analysis of longitudinal data. Descriptive statistics were used to report baseline participants' characteristics. Normally distributed variables (according to a Shapiro–Wilk test and visual inspection of histograms, Q-Q plots and box plots), are presented as the mean with SD, non-normally distributed variables are presented as the median and interquartile range (IQR), and categorical variables are expressed as frequencies (%). The independent-samples t test was used to compare normally distributed variables from two independent groups of equal variances, and Mann–Whitney U-test or chi^2-test was used for analysis of non-parametric variables. For analysis of differences between dependent groups Wilcoxon signed ranks test was used.

Because BNP values were positively skewed, they were log-transformed to allow for further statistical analysis. Pearson's product moment correlation was used for analysis of parametric variables and Spearman's rho was used for analyses of correlations between nonparametric variables. Then multiple linear regression analysis employing backward step multivariate analysis, excluding variables that were not significant and did not improve the fit of the model, was used. In analysis of the longitudinal data, the relation between ROH and log-BNP was analyzed with a mixed model using ROH as a fixed effect (same slope) and individuals as random effect (different intercepts). Statistical significance was inferred at ≤0.05.

RESULTS

Of 81 eligible individuals, five did not fulfill the inclusion criteria, seven declined to participate, and five dropped out after enrollment due to renal transplantation (n = 1), recovery (n = 1), transferal to peritoneal dialysis (n = 1) or death (n = 2). Overall, 64 individuals participated in the first analysis.

The median (IQR) BNP value was 365 (178–833) pg/mL for the entire cohort. BNP levels were above 500 in 38% (n = 24) of the participants, with a median value of 1060 (815–2300) pg/mL. This group (h-BNP) had a 15 ± 6.2% ROH before dialysis, corresponding to an AOH of 2.5 (1.8–4.6) L. Participants with BNP values below 500 pg/mL (l-BNP) had a median value of 208 (117–344) pg/mL, 9.5 ± 6.2% ROH and 1.9 (1.0–2.5) L AOH. The differences in both ROH and AOH between the groups were significant, and a small but significant difference in reported symptoms of overhydration was also found. In h-BNP, but not in l-BNP, there was a significant difference between normohydration weight (according to bioimpedance) and prescribed dry weight. Ultrafiltration volumes and rates did not differ between the groups, and there were no differences in blood pressure. In l-BNP every third participant experienced clinically symptomatic intradialytic hypotension. In h-BNP the number was lower, 20.8% (n = 5), however this difference was not statistically significant (Table 1).

In l-BNP, the average treatment time was 4.5 hours, 100% were treated with high permeable dialyzers, and 80% (n = 32) treated with hemodiafiltration (HDF). In h-BNP, the average treatment time was 4 hours, 74% (n = 17) were treated with high permeable dialyzers, and only 58% (n = 14) treated with HDF, but no difference in number of treatments per week or in small-solute clearance was found. In h-BNP, half of patients had diabetes type 2, and compared to the l-BNP group, the h-BNP group was older, had less muscle strength, lower lean tissue index, lower body weight, and lower levels of hemoglobin and albumin. CRP was higher in h-BNP, but no other inflammatory markers differed significantly (Table 1).

As illustrated in Figure 1, a positive correlation was found between log-BNP and ROH (r_s = 0.380, $P < 0.01$). Log-BNP also correlated positively with age, CRP, and symptoms of overhydration, but negatively to handgrip strength, hemoglobin and albumin (Table 2). On multiple linear backward regression analysis ROH, albumin and age remained significantly associated with log-BNP (Table 3).

Twenty-four individuals fulfilled the criteria for the longitudinal follow-up (BNP > 500). Of these, seven were excluded because they were not on thrice-weekly dialysis, two declined to participate, and four died before enrollment, leaving 11 participants who were further assessed in another nine dialysis sessions each.

No significant difference in prevalence of heart disease, as registered in the medical records, was found between the h-BNP and l-BNP groups (Table 1). However, when examined, none of the 11 participants in the longitudinal follow-up had a normal echocardiography; four had left ventricular hypertrophy and five had an ejection fraction under 55% indicating systolic cardiac failure. Signs of diastolic dysfunction were seen in seven participants, and five had pulmonary hypertension. In four of these participants HRV could not be analyzed due to pacemaker treatment or atrial fibrillation or flutter. In the remaining seven subjects the cardiac autonomic function was markedly decreased, as illustrated by the low SDNN (Table 4).

Figure 2 shows the variation of BNP and ROH in repeated measurements of 11 subjects. Although the confidence intervals in both BNP and ROH are wide, the significant correlation between log-BNP and ROH remained when it was studied on an individual level in repeated measurements (Figure 3).

In analysis of the relationship between ROH and log-BNP, using a mixed method model with same slope, different intercepts, every percentage point increase of ROH predicted an increase in log-BNP by 5%, and between-individuals variation was greater SD = 0.581 than within-person variation SD = 0.285.

DISCUSSION

Hemodialysis patients with both overhydration and high levels of BNP are at increased risk for all-cause mortality.[14,42] Compared to previous reports,[1] our study cohort of 64 hemodialysis patients was relatively well fluid adjusted, with only a modest ROH of 11.6 ± 6.7% in the whole group. Despite this, and the low number of subjects in the h-BNP group (24 participants), a statistically significant correlation was found between overhydration and BNP. The h-BNP group had a 15 ± 6.2% ROH, which was 58% more than the l-BNP group.

In the correlation between BNP and overhydration the r value was only 0.38, and ROH accounted only for 14% of the variance in log-BNP. Furthermore, some individuals were severely overhydrated without having increased levels of BNP, thus, a normal BNP does not rule out overhydration as defined by bioimpedance in hemodialysis patients. However, when albumin and age were added to a regression model, the model could explain 47% of the variation in log-BNP. Compared to the l-BNP group, the h-BNP group had less muscle strength, lower body

Table 1 Baseline clinical characteristics of study sample

Variable	All participants (N = 64)		Differences between groups				
			BNP < 500 (N = 40)		BNP > 500 (N = 24)		P value
Men	76.6%	(n = 49)	77.5%	(n = 31)	75%	(n = 18)	0.82
Age	71	(60–79)	67	(54.5–76.5)	77	(71–83)	0.001**
Weight (kg)	82.4	±18.3	86.0	±18.4	76.4	±16.9	0.041*
Dialysis vintage (months)	37	(16–75)	34.5	(19–82)	44	(13–74)	0.70
BP systolic (mmHg)	143.8	±26.2	143.6	±27.6	144.0	±24.1	0.953
BP diastolic (mmHg)	66.7	±16.3	68.1	±16.5	64.5	±16.0	0.403
StdKt/V	2.4	(2.3–2.6)	2.4	(2.2–2.6)	2.4	(2.3–2.6)	0.912
Comorbidities							
Diabetes type 1	7.8%	(n = 5)	10%	(n = 4)	4.2%	(n = 1)	0.40
Diabetes type 2	39.1%	(n = 25)	30%	(n = 12)	54.2%	(n = 13)	0.055
Ischemic heart disease	29.7%	(n = 19)	27.5%	(n = 11)	33.3%	(n = 8)	0.62
Other heart disease	32.8%	(n = 21)	30%	(n = 12)	37.5%	(n = 9)	0.54
Laboratory test results							
CRP (mg/L)	7.05	(2.7–18)	4.6	(1.8–18)	11.5	(3.7–21)	0.049*
Hemoglobin (g/L)	109.3	±13.4	113.7	±12.3	101.8	±12.0	0.000**
Albumin (g/L)	30.3	±4.3	32	±3.5	27.7	±4.2	0.000**
Phosphorus (mmol/L)	1.5	±0.5	1.5	±0.5	1.6	±0.5	0.544
BNP (pg/mL)	365	(178–833)	208	(117–344)	1060	(815–2300)	0.000**
Inflammatory markers							
Endostat (pg/mL)	78,609	(68,568–87,715)	79,373.5	(66,859–85,475)	76,877	(71,728–92,236)	0.53
IL6 (pg/mL)	5	(5–9)	5	(5–5)	5	(5–11.6)	0.54
TNFalfa (pg/mL)	14.87	(12.7–19)	14.87	(12.7–17.9)	15.42	(13–19.3)	0.58
MMP9 (pg/mL)	26,731	(18,471–40,709)	29,711	(18,659–41,573)	24,329	(13,928–36,432)	0.19
Gal 3 (pg/mL)	8659	(6531–10,330	8659	(6370–10,269)	8543.5	(6531–11,079)	0.88
TNFr1 (pg/mL)	13,962	(10,964–18,338)	13,447.5	(10,964–17,707)	16,158.5	(11,108–22,866)	0.28
TNFr2 (pg/mL)	21,686	18,534–24,458)	20,502	(18,350–23,518)	21,996	(21,158–26,552)	0.09
Cath L (pg/mL)	8871	6955–10,916)	8572.5	(6721–10,834)	9268	(7975–11,360)	0.13
Cath S (pg/mL)	3440	(2715–3803)	3450	(2715–3875)	3351	(2692–3732)	0.57
IL1 Beta (pg/mL)	1	(1–1)	1	(1–1)	1	(1–2.2)	1.00
Naprilysin (pg/mL)	473.5	(160–2304)	561.5	(165–3028)	381	(160–1656)	0.47
IL 10 (pg/mL)	18.6	(7.5–64)	18.6	(7.5–52)	22.3	(15–95.4)	0.78

Treatment prescriptions							
Hours/treatment	4.5	(4–4.5)	4.5	(4–4.9)	4	(4–4.5)	0.032*
Treatments/week	3	(3–3)	3	(3–3)	3	(3–3)	0.33
Hemodiafiltration	71.9%	(n = 46)	80%	(n = 32)	58.4%	(n = 14)	0.062
High permeable dialyzer	87.5%	(n = 56)	100%	(n = 39)	73.9%	(n = 17)	0.001**
Volume status							
Absolute OH (L)	2.0	(1.2–3.2)	1.9	(1.0–2.5)	2.5	(1.8–4.6)	0.010*
Relative OH (%)	11.6	±6.7	9.5	±6.2	15.0	±6.2	0.001**
NH weight (kg)	80.1	±18.4	84.1	±18.5	73.6	±16.6	0.026*
Dry weight (kg)	80.1	±18.6	83.7	±18.8	74.5	±17.4	0.071
UFV (L)	2.1	(0.9–2.7)	1.7	(0.8–2.9)	2.3	(0.9–2.6)	0.96
TBW (L)	37.6	±6.8	39.4	±6.3	34.7	±6.7	0.007**
ECW (L)	19.1	±3.5	19.6	±3.3	18.3	±3.6	0.161
ICW (L)	18.5	±3.7	19.8	±3.4	16.4	±3.3	0.000**
E/I	1.0	±0.1	0.99	±0.11	1.1	±0.1	0.000**
Symptoms, OH	0.5	(0–2)	0	(0–2)	2	(0–2)	0.017*
Symptoms, fluid depletion	−1	(−3–0)	−1	(−4–0)	0	(−2–0)	0.298
Intradialytic hypotension	28.6%	(n = 18)	33.3%	(n = 13)	20.8%	(n = 5)	0.392
Nutritional status							
Handgrip (kg)	24	(20–36)	28.5	(20–37)	22	(17.5–27)	0.046*
BMI (kg/m^2)	27.3	±5.4	28.3	±5.5	25.7	±5.0	0.059
LTI (kg/m^2)	11.6	±2.5	12.4	±2.4	10.3	±2.2	0.001**
FTI (kg/m^2)	14.8	±5.4	15.4	±5.4	14.0	±5.5	0.324

Data are expressed as mean ± SD, median with (inter quartile range), or percent frequency; and differences between groups are tested for significance with independent-samples t test, Mann-Whitney U test or chi-square, as appropriate.

BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; CRP = serum C-reactive protein; E/I = ECW/ICW; ECW = extra cellular water; FTI = fat tissue index; ICW = intra cellular water; LTI = lean tissue index; OH = overhydration; StdKt/V = standard Kt/V; TBW = total body water; UFV = ultrafiltration volume.

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

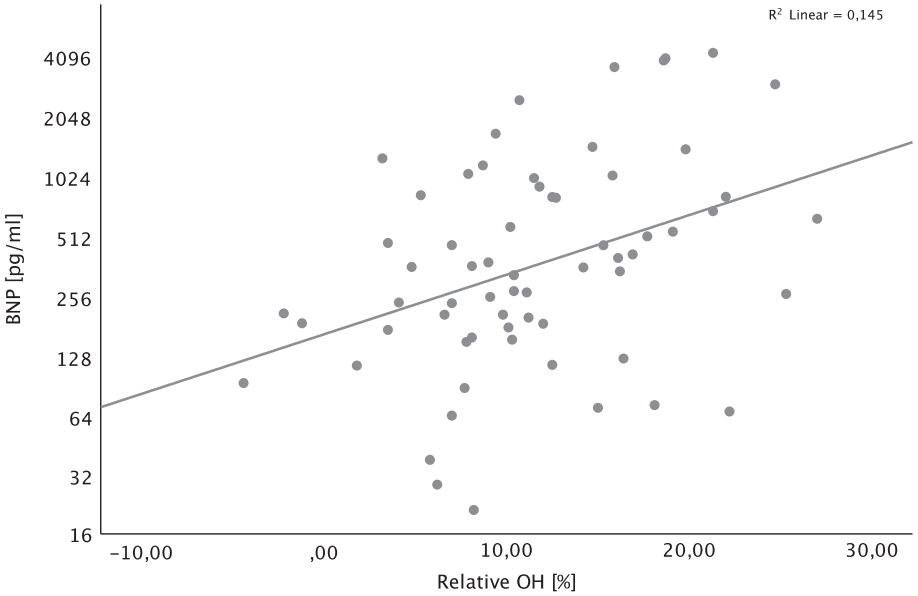

Figure 1 Correlation (r_s = 0.380; P < 0.01) between log-transformed brain natriuretic peptide (BNP) and relative overhydration in a cohort of 64 hemodialysis patients.

weight, lower lean tissue index and lower levels of hemoglobin and albumin, but higher CRP levels. These findings indicate malnutrition and inflammation, which have been associated with overhydration.[4,43–46] However, although the h-BNP group had higher CRP levels, we were not able to confirm the association between overhydration and IL-6 and TNF-alpha or any other inflammatory markers, which has been found in studies with larger samples.[45]

We found that the dry weight was set higher than the normohydration weight (according to bioimpedance) in the h-BNP group, 74.5 kg vs. 73.6 kg, while set lower than normohydration weight in the l-BNP patient group, 83.7 kg vs. 84.1 kg. Compared to the l-BNP patient group the patients in the h-BNP had considerably lower body weight. Previously an inverse relationship has been established between overhydration and obesity in hemodialysis patients.[43,47] However, in healthy subjects there is no evidence of systematic bias in bioimpedance-measured overhydration with high bodyweight.[48] It is possible that our finding is explained by physician bias; it may be easier to believe that an overweight patient, rather than a lean patient, should have reduced dry weight. Thus, obesity seems to offer some protection from overhydration in hemodialysis patients, which may then be one explanation to the obesity paradox; obesity being protective for all-cause mortality in hemodialysis patients.[49]

No correlation was found between BNP and blood pressure, and blood pressure did not correlate with hydration status either. In clinical assessment of hydration status, blood pressure is often used as a marker of overhydration,[50] but although sodium retention and volume overload are considered the prominent pathogenic mechanisms of hypertension in hemodialysis patients, a number of nonvolume mediated pathways may also play important roles in the complex pathogenesis of hypertension.[51–53] It has been argued that BNP cannot predict the amount of fluid to be removed, as its relationship with blood pressure is not due to volume.[24,27] However, our results, in line with other reports, question the use of blood pressure guided fluid management.[1,38]

BNP levels vary considerably across the dialysis population, and may be affected by both pathologic cardiac structure and function, treatment modalities and adverse events during dialysis.[23,28] For this reason, in our longitudinal follow-up patients with less than three treatments per week were not included, and all remaining participants were transferred to treatment with high permeable dialyzers. We found however that this change had no affect on the predialysis BNP levels (Supporting Information Table S1); also did not small-solute clearance differentiate between h-BNP and l-BNP groups, despite difference in treatment times. Thus, it is unlikely that treatment time, or clearance of biomarkers explain differences in levels of BNP in our study sample to any larger extent. However, echocardiographic pathologies were present in all 11 participants in the longitudinal follow up, and decreased HRV was found in a subset of the group.

Because BNP and bioimpedance parameters have been found to remain relatively stable within individuals over time,[31] measurement of BNP may be better applied in the

Table 2 Correlations in a cohort of 64 individuals on hemodialysis

	Relative OH	Absolute OH	Symptoms OH	BP systolic	BP diastolic	Age	Hand grip	CRP	Hemoglobin	Albumin
Log-BNP	0.380**	0.324**	0.278*	−0.091	−0.259*	0.562**	−0.277*	0.276*	−0.349**	−0.493**
Rel. OH		0.946**	0.537**	−0.134	−0.118	0.046	−0.012	0.155	−0.272*	−0.263*
Abs. OH			0.569**	−0.105	−0.082	0.006	0.145	0.112	−0.260*	−0.225
Symptoms OH				0.188	0.217	0.037	0.220	0.103	−0.390**	−0.115
BP systolic					0.651**	−0.013	0.223	−0.211	−0.180	0.222
BP diastolic						−0.399**	0.409**	−0.151	−0.109	0.267*
Age							−0.273*	0.028	−0.076	−0.275*
Hand grip								−0.093	0.049	0.315*
CRP									−0.282*	−0.452**
Hb										0.368**

Analysis performed with Spearman's rho, for bivariate analyses of nonparametric variables, or with Pearson's product moment correlation for parametric variables.
BNP = brain natriuretic peptide; BP = blood pressure; CRP = serum C-reactive protein; Hb = hemoglobin; OH = overhydration.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 3 Multiple regression model for log-BNP pre dialysis

Variable	Crude analysis		Adjusted analysis	
	Slope	P	Slope	P
ROH	0.069	0.002	0.066	0.001
Albumin	−0.14	0.000	−0.093	0.003
Age	0.047	0.000	0.041	0.000

Adjusted r^2 value for model 0.471.
ROH = relative overhydration.

dialysis population using a relative-change strategy rather than by comparing absolute values to a reference interval or threshold value.[24,32,54] The results of our study support these findings, as our main finding was that the variation in BNP reflected the variation in ROH in repeated measurements, and the between-individuals variation of BNP in relation to overhydration was larger than the within-individual variation. The great difference in intercepts in the mixed methods analysis may be explained by the patients' degree of heart failure, nutritional status, and occurrence of inflammation.

Table 4 Mean values of heart rate variability (HRV) and frequencies of cardiac dysfunction in participants with elevated BNP

Variable		
HRV		(N = 7)
SDNN (ms)	51.7	± 24.7
RMSSD (ms)	49.2	± 29.9
pNN50 (%)	8.92	(5.36–46.1)
ULF (ms^2)	465.1	(94.5–6307.2)
VLF (ms^2)	366.1	(106.7–3273.5)
LF (ms^2)	176.8	(59.6–1128.1)
HF (ms^2)	364.3	(114.5–910.7)
log LF/HF ratio	−0.2	(−0.8–0.9)
Total power (Hz)	1273.9	(394.0–10,276.0)
Echocardiographic findings		(N = 11)
Left ventricular hypertrophy	36.4%	(n = 4)
Systolic dysfunction	45.5%	(n = 5)
Diastolic dysfunction	63.6%	(n = 7)
Heart rate	76	(65–90)
Sinus rhythm (no)	36.4%	(n = 4)
Regional hypokinesia	54.5%	(n = 6)
Pulmonary hypertension	45.5%	(n = 5)

HF = high frequency (0.15–0.4 Hz); LF = low frequency (0.04–0.15 Hz); NN = interval between two heartbeats; pNN50 = the percentage of successive intervals that differ by more than 50 ms; VLF = very low frequency (0.00–0.04 Hz); RMSSD = the square root of the root mean square of the sum of all differences between successive NN intervals; SDNN = standard deviation of all NN intervals.

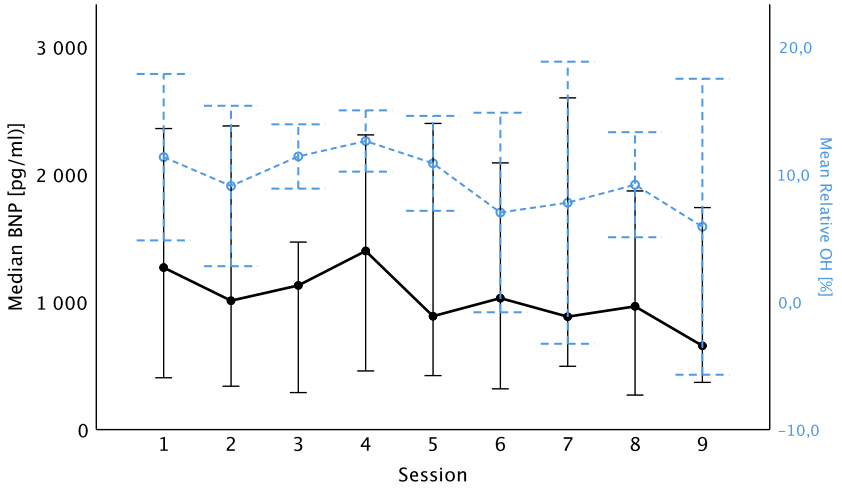

Figure 2 Predialytic changes in brain natriuretic peptide (BNP, black interpolation line) expressed as median and relative overhydration (Rel OH, dotted interpolation line) expressed as mean, from first second and third study week. Error bars: 95% confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

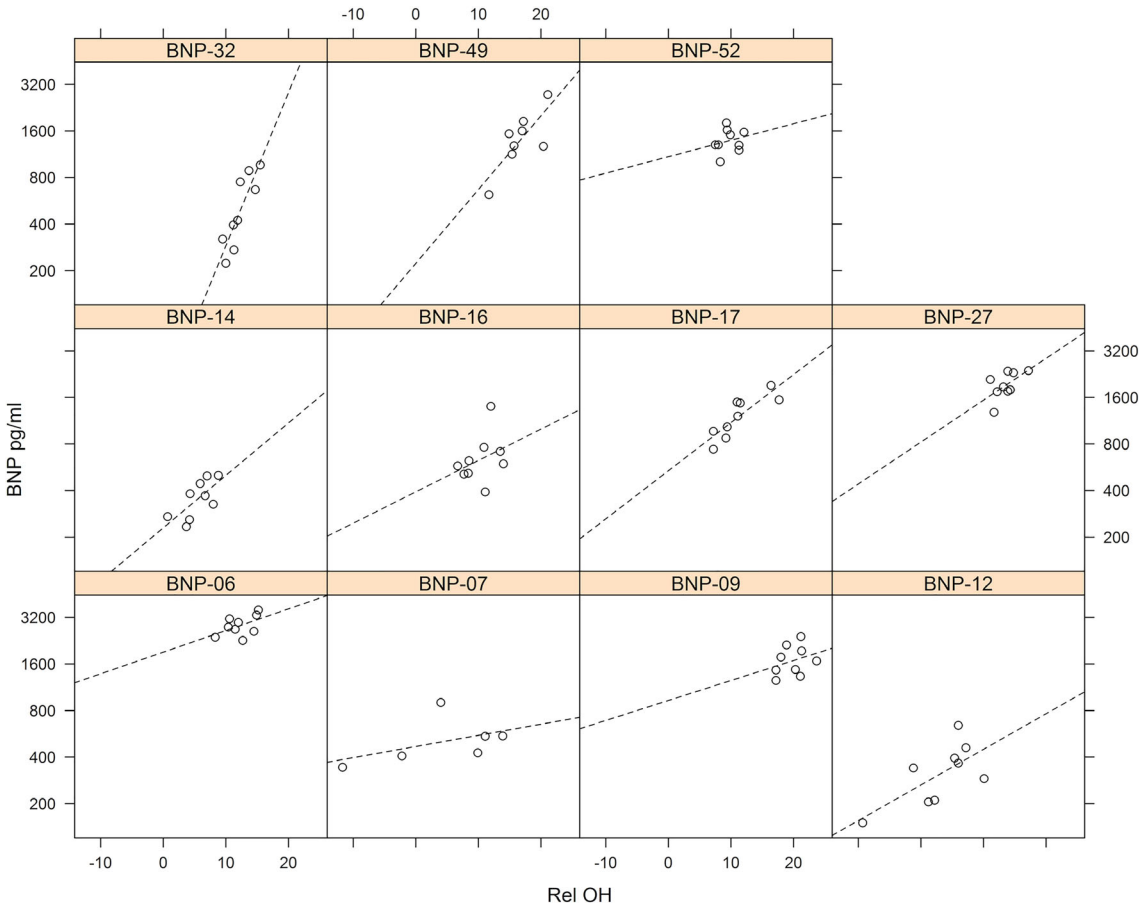

Figure 3 Correlation between log-transformed brain natriuretic peptide (BNP) and relative overhydration (Rel OH) in repeated measurements in 11 individuals. [Color figure can be viewed at wileyonlinelibrary.com]

LIMITATIONS

This study has several limitations. It is observational, and the participants were recruited from a hemodialysis center where residual renal function, which may affect BNP levels,[55] was not routinely measured. Also, the study sample is relatively small, and due to the study design and for reasons of feasibility, cardiac function was examined only in the h-BNP group. Hence, we are not able to tell if the abnormalities demonstrated in cardiac evaluation of the 11 patients in the h-BNP group, are due to fluid overload, or other cardiac pathology. Examination of cardiac function in the l-BNP group could have added valuable information.

For assessment of symptoms of overhydration, we used a score system[39,40] without a validated Swedish translation. However, to our knowledge no validated tools for assessment of symptoms of overhydration exist, but use of a previous score system enables international comparisons. Another limitation is that we used bioimpedance as the reference for overhydration. In a recent review Covic et al.[15] conclude bioimpedance-based interventions for correction of overhydration, in end stage renal disease patients, may have little to no effect on all-cause mortality. However, the size and power of the randomized controlled trials included in the review were low, and the results were conflicting. To our knowledge, no universally accepted definition of overhydration exists. Whereas bioimpedance has been thoroughly validated in the hemodialysis population,[9–11] is readily available, and acknowledged a clinically useful tool,[56] we chose to use it for measuring hydration status.

CONCLUSIONS

In this prospective observational study we found that BNP correlated not only with overhydration, but also with CRP and malnutrition. BNP might serve as a marker of overhydration in a subgroup of predominantly elderly and malnourished hemodialysis patients. Although overhydration accounted only for a small variance in BNP, our study demonstrates that BNP reflects individual variation in hydration status over time. Thus we conclude BNP seems to be a modifiable marker of overhydration, best applied for measuring changes in hydration status within an individual. Studies with larger samples are required to confirm these findings.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Differences between baseline observations and second observation point of second phase, in 11 individuals included in the second phase of the study. Significance of differences tested with Wilcoxon signed ranks test.