B-type natriuretic peptide is not a volume marker among patients on hemodialysis

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ABSTRACT

Background. Although the cardiac biomarker B-type natriuretic peptide (BNP) is strongly related to mortality in end-stage renal disease (ESRD), whether it is a predictor of weight change or blood pressure (BP) response upon probing dry weight among hypertensive hemodialysis patients remains unknown. The purpose of this study was to examine among people with hypertension on hemodialysis whether BNP is a biomarker of excess volume.

Methods. Hypertensive hemodialysis patients \((n=150)\) were randomized to a control group \((n=50)\) or an ultrafiltration group \((n=100)\) and followed up for 30 dialysis treatments. After a baseline run-in of six treatments, those assigned to the ultrafiltration group had dry weight probed over 8 weeks. Forty-four-hour interdialytic ambulatory BP and predialysis BNP were measured at the end of run-in period, at 4 weeks and at 8 weeks.

Results. The median BNP concentration was 93 pg/mL (interquartile range 31–257 pg/mL). The magnitude of decline in the BNP depended on the baseline concentration of BNP, but did not require probing dry weight or weight loss. No relationship existed between decline in postdialysis weight upon probing dry weight and baseline BNP. Furthermore, reduction in the BNP was not required for decline in systolic ambulatory BP. Predialysis log BNP modestly predicted ambulatory systolic and pulse pressure independently of other risk factors. No relationship was found between decline in BP upon probing dry weight and baseline BNP. Upon probing dry weight, reduction in BNP was not required for decline in systolic ambulatory BP.

Conclusion. Taken together, these data suggest that among hypertensive patients on hemodialysis BNP is not a volume marker.

INTRODUCTION

The quest for biomarkers of volume excess continues [1, 2]. Among hemodialysis patients, this search is of particular importance because occult volume overload is common and accounts for a large burden of volume-related hospitalizations. Several such markers have been reported such as body impedance analysis [3], relative plasma volume monitoring [4, 5], echocardiographic markers [6] and some blood biomarkers [7]. Biomarkers in the blood have several advantages over other markers, in that they are commercially available and standardized; their use can be a convenient way to assess volume excess.

A growing interest has emerged in the evaluation among patients with end-stage renal disease (ESRD) of cardiac natriuretic peptides such as atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Soon after the discovery of natriuretic peptides in the mid 1980’s, there was an interest in the use of these biomarkers for the diagnosis of volume excess. The first few reports in the English language literature all evaluated ANPs. For example, Leunissen et al. studied 19 chronic hemodialysis patients and found a strong relationship between inferior vena cava diameter and ANP [8]. Lauster et al. studied ANP and cyclic GMP before and after dialysis and found among 20 chronic hemodialysis patients a strong correlation between clinically assessed excess volume and pre- and postdialysis levels of these biomarkers [9]. The same group in a report 2 years later concluded that the plasma cGMP level after hemodialysis is more apt for the determination of dry body weight than ANP [10]. However, another group found that cGMP values are less informative, and ANP does not provide any information at all on the clinical assessment of dry weight [11]. None of these early reports measured BNP or evaluated left ventricular mass or function by echocardiograms.

When echocardiograms were performed in a group of 246 Italian hemodialysis patients without overt heart failure, both ANP and BNP were noted to be strongly related to left ventricular mass and function [12, 13]. These reports lead to the conclusion that measuring the plasma concentration of cardiac natriuretic hormones, particularly BNP, may be useful for the identification of hemodialysis patients with left ventricular hypertrophy or for excluding systolic dysfunction. Furthermore,
these reports concluded that it is unlikely that cardiac natriuretic peptides are of use to determine dry weight [12].

Several investigations among hemodialysis patients have sought to evaluate the utility of BNP or NT-proBNP as independent markers of volume [14–19]. Some of these studies have found these markers to be useful [14, 18, 19]; others, not so [15, 16, 18] but they all have limitations. All these studies have been small, ranging from 32 to 72 patients. Furthermore, the reference standard for fluid excess in four of these six studies was made by bioimpedance analysis [14, 15, 17, 18]. It is now recognized that BNP levels are strongly related to lean body mass [20] and inversely to obesity [21]. Thus, bioimpedance may be fraught with errors in evaluating the value of natriuretic peptides in patients on hemodialysis. Finally, all these studies have been cross-sectional, making it difficult to imply a cause and effect relationship.

Given that the majority of hypertensive patients on hemodialysis have occult or manifest volume overload, it is biologically plausible that if BNP is related to volume, then a higher BNP level upon probing dry weight might be related to greater decline in BNP, more weight loss and more improvement in blood pressure (BP). Accordingly, the hypothesis that BNP is a marker of volume among hypertensive hemodialysis patients upon probing dry weight was tested as a prespecified analysis of the dry-weight reduction in hypertensive hemodialysis patients (DRIP) trial [22].

### MATERIALS AND METHODS

#### Participants

Details of the DRIP trial have been previously reported [22]. Briefly, we recruited patients 18 years of age or older on long-term hemodialysis for at least 3 months, who had hypertension defined as a mean interdialytic ambulatory BP of ≥135/85 mmHg. After a six-hemodialysis run-in phase, during which baseline data were collected, patients were randomized in 1:2 proportion to a control group versus an ultrafiltration trial group for 8 weeks. Pre- and post-BP and weights were averaged over these six-treatment run-in phases. During this 24-dialysis treatment phase, patients were seen at each dialysis visit and had dry weight探測 as assessed by symptoms and signs related to hypovolemia [23, 24]. The ultrafiltration group underwent an additional weight loss of 0.1/10 kg body weight per dialysis without increasing the time or frequency of dialysis. This additional weight loss was combined with the ultrafiltration volume required to remove interdialytic weight gain to achieve the desired reduction in dry weight. If ultrafiltration was not tolerated based on the symptoms and signs such as muscle cramps, need for excessive saline or symptomatic hypotension, the additional prescribed weight loss was reduced by 50%. If ultrafiltration was still not tolerated, the additional weight loss was further reduced by 50% until even 0.2 kg incremental weight loss per dialysis was not tolerated. At this point, the patient was said to be at his or her dry weight. Thus, by this protocol, each patient had to experience symptoms of volume depletion to be at dry weight. The control group had regular physician visits but no additional reduction in dry weight. No changes in antihypertensive medication were permitted during the trial.

#### Blood pressure monitoring

Ambulatory BP monitoring was performed after the midweek hemodialysis session for 44 h at baseline and at 4 and 8 weeks. Blood pressures were recorded every 20 min during the day (6 AM–10 PM) and every 30 min during the night (10 PM–6 AM) using a Spacelab 90207 ABP monitor (SpaceLabs Medical Inc, Redmond, WA) in the non-access arm. Recordings began immediately after hemodialysis and terminated immediately before the subsequent dialysis. Accuracy of ambulatory BP recordings was confirmed against auscultated BP at baseline. Hourly means were calculated. These means were then averaged over the entire course of recording to provide systolic and diastolic interdialytic ambulatory BPs. The mean interdialytic ambulatory BP served as the reference standard.

#### Biomarkers

All laboratory measurements were done before dialysis and the specimen was obtained from the patient’s arterio-venous access or tunneled dialysis catheter for hemodialysis. The BNP was measured using the ADVIA Centaur XP Automated Chemiluminescence System (Siemens Healthcare, Erlangen, Germany) using a kit from the same manufacturer. BNP levels <100 pg/mL are considered normal, and the detection limits range from 2 to 5000 pg/mL.

#### Statistical analyses

BNP data at baseline were dichotomized about the median and resulting groups were compared using the chi-squared test for discrete variables or t-tests for continuous variables.

A mixed model was used to allow for repeated measurements within individuals as previously reported [25]. To assess time course of BNP, a model was fitted with BNP as the dependent variable. Given the skewed distribution of BNP, it was natural log-transformed for all analyses to approximate a normal distribution. For this model, the fixed independent variables were two indicator variables and one continuous variable. The indicator variables were group (with two levels: ultrafiltration and control), and visits (with three levels: baseline, 4 and 8 weeks) and the continuous variable was the baseline log BNP. All possible two-way and three-way interactions for the three terms were entered into the model. Random variables were subject and visits and the covariance was modeled as unstructured to allow for the slopes and intercepts to vary independently of each other. After fitting this model, the least square means were calculated at baseline, Weeks 4 and 8 for the control and ultrafiltration groups for each instance of baseline BNP concentrations in a graded fashion over a range from 100 to 1000 pg/mL.

To assess the overall value of baseline BNP to predict change from baseline in postdialysis weight on probing dry weight, two models were compared using the likelihood ratio test. The dependent variable for each of these two models was the change from baseline in postdialysis weight. In the first model, the independent indicator variables were group and...
weeks and their interactions. The second model, in addition to model one, contained the continuous variable of baseline log BNP and its two-way and three-way interactions with group and weeks.

To assess the overall value of change in BNP to predict interdialytic ambulatory systolic BP on probing dry weight, two models were compared using the likelihood ratio test. The dependent variable for each of these two models was the change from baseline in systolic BP. In the first model, the independent indicator variables were group and weeks and their interactions. The second model, in addition to model one contained the continuous variable of change from the baseline log BNP and its two-way and three-way interactions with group and weeks. In addition, adjustment was made for the baseline BNP.

To facilitate data interpretation, presented in the figures are the least square means. The Wald test was used to compare changes after fitting the mixed model.

All analyses were conducted using Stata 11.2 (College Station, TX). The P-values reported are two-sided and insignificant at <0.05.

RESULTS

Table 1 shows the baseline clinical characteristics of the study population dichotomized at median BNP concentration. The median BNP concentration was 93 pg/mL (interquartile range 31–257 pg/mL). Twenty-four predialysis samples were missing; therefore, there were 63 observations in each group. Importantly, the assignment to ultrafiltration and control groups was balanced between groups. Most of the baseline characteristics were well matched, except for diabetes, smoking, weight and body mass index.

Time trends in change in BNP

The time trend of log BNP by group assignment (control or ultrafiltration) is shown in Figure 1A and B. In Figure 1A, the dashed lines represent the control group and the solid line the ultrafiltration group. A significant drop from baseline in BNP was noted over weeks (P = 0.002). The decline in BNP was dependent on the baseline concentration of BNP (P < 0.0001). This change was seen in the control group (P = 0.017) with no additional contribution by ultrafiltration (P = 0.5). Figure 1B shows that at low levels of BNP, little change in BNP at 4 and 8 weeks is noted; the 95% confidence interval of the change crosses zero. At higher BNP levels, there was a decline in BNP at 4 and 8 weeks. Declines in BNP in the ultrafiltration group were also noted at 4 and 8 weeks, but the magnitude of these changes which ranged from 25 to 75% was not significantly different from the control group.

BNP as a predictor of postdialysis weight change on probing dry weight

To assess the overall value of the baseline BNP to predict postdialysis weight on probing dry weight, two models were compared using the likelihood ratio test, one with BNP and one without. The likelihood ratio test to compare models was not significant (P = 0.9). The results of this model are shown in Figure 2A. For neither the control nor the ultrafiltration group was the baseline BNP predictive of change from baseline in systolic BP at 4 or 8 weeks.

To assess the overall value of change in BNP to predict postdialysis weight on probing dry weight, two models, one containing change in BNP and one not, were compared using the likelihood ratio test. The likelihood ratio test to compare models was not significant (P = 0.48). (B) shows the change from baseline in postdialysis weight for fold change in BNP concentration adjusted for the baseline BNP. The modeled changes are plotted at the log mean BNP at baseline of 92 pg/mL. For 1-fold change, which can be interpreted as no change from baseline, there was a decline in postdialysis weight seen in the ultrafiltration group at both 4 and 8 weeks. Similar results were evident when there was 90% reduction from baseline in BNP (0.1-fold change). Thus, the BNP change was not statistically predictive of change in postdialysis weight for either group.

BNP as a predictor of BP response to probing dry weight

The relationship between BNP with systolic 44-h ambulatory BP is shown in Figure 3. Figure 3A shows the relationship of log BNP measured at baseline with systolic BP at baseline. Least squares regression revealed the beta coefficient of 1.2 mmHg/log BNP, se 0.51, P = 0.02. Multivariate adjustment for age, sex, race, diabetes, smoking and body mass index did not remove the association between BNP and systolic BP (β = 1.14, se 0.55, P = 0.04). Diastolic ambulatory BP was not related to log BNP (β = −0.57, se 0.54, P = 0.29). Pulse pressure, on the other hand, was related to log BNP (β = 1.76, se 0.68, P = 0.01) and remained significant after multivariate adjustment (β = 1.70, se 0.59, P = 0.004). Even further adjustment for systolic BP retained the significance of log BNP on pulse pressure (β = 0.94, se 0.47, P = 0.047).

Figure 3B and C show the relationships of baseline BNP with BP at 4 and 8 weeks, respectively. The bivariate relationship remained strong for the control group (dashed line), but weakened for the ultrafiltration group (solid line).

Figure 3D shows the relationships of BNP measured at 4 weeks with BP measured at 4 weeks. Figure 3E shows these relationships at 8 weeks. Although significant at 4 weeks, at 8 weeks the relationship between BP and log BNP was not significant for the ultrafiltration group. At Week 8, in the case of the ultrafiltration group, the slope was nearly flat (β = 0.1126, P = 0.92).

BNP as a predictor of BP response to probing dry weight

The likelihood ratio test to compare models with and without baseline log BNP was not significant (P = 0.15). Thus, the baseline log BNP was not predictive of BP change from baseline. The results of this model are shown in Figure 4A. For neither the control nor the ultrafiltration group was baseline BNP predictive of change from baseline in systolic BP at 4 weeks. At 8 weeks, the results were similarly negative. For every log unit higher baseline BNP, there was 2.47 mmHg higher BP at 8 weeks in the control group (P = 0.058). For every log unit higher baseline BNP, there was 0.27 mmHg
lower BP at 8 weeks (P = 0.8) in the ultrafiltration group (between group difference, P = 0.09).

To assess the overall value of change in BNP to predict BP on probing dry weight, two models, one containing change in BNP and one not were compared using the likelihood ratio test. The likelihood ratio test to compare models was not significant (P = 0.061). Thus, the change in BNP was not predictive of decline in systolic BP. Figure 4B shows the change from

<table>
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<th>Variable</th>
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<th>More than median BNP</th>
<th>P-value</th>
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<td>BNP (pg/mL)</td>
<td>34 ± 25</td>
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<td>Ultrafiltration group, n (%)</td>
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<td>41 (65.1%)</td>
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<td>Age (years)</td>
<td>54.2 ± 12.2</td>
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<td>Men n (%)</td>
<td>42 (66.7%)</td>
<td>43 (68.3%)</td>
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<td>Blacks n (%)</td>
<td>55 (87.3%)</td>
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<td>Diabetes mellitus n (%)</td>
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<td>13 (20.6%)</td>
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<td>1 (1.6%)</td>
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<td>Stroke n (%)</td>
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<td>4 (6.3%)</td>
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<td>28 (44.4%)</td>
<td>36 (57.1%)</td>
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<tr>
<td>Angiotensin receptor blocker n (%)</td>
<td>6 (9.5%)</td>
<td>13 (20.6%)</td>
<td>0.08</td>
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<td>Hemoglobin (g/dL)</td>
<td>12.3 ± 1.1</td>
<td>12.1 ± 1.5</td>
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<td>Serum albumin (g/dL)</td>
<td>3.7 ± 0.4</td>
<td>3.6 ± 0.5</td>
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<td>Serum creatinine (mg/dL)</td>
<td>9.6 ± 2.9</td>
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<td>Serum potassium (mEq/L)</td>
<td>4.6 ± 0.6</td>
<td>4.5 ± 0.6</td>
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<td>Serum calcium (mg/dL)</td>
<td>9 ± 0.7</td>
<td>8.9 ± 0.7</td>
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<td>Serum phosphorus (mg/dL)</td>
<td>5.2 ± 1.4</td>
<td>5.4 ± 1.7</td>
<td>0.59</td>
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<td>Predialysis blood urea nitrogen (mg/dL)</td>
<td>50.6 ± 15.2</td>
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<td>Postdialysis blood urea nitrogen (mg/dL)</td>
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<td>Urea reduction ratio (%)</td>
<td>74.1 ± 7.3</td>
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<td>Predialysis weight (kg)</td>
<td>88.4 ± 20.3</td>
<td>81.3 ± 17.8</td>
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<td>Postdialysis weight (kg)</td>
<td>85.4 ± 19.7</td>
<td>78.4 ± 17.3</td>
<td>0.04</td>
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<tr>
<td>Estimated dry weight (kg)</td>
<td>85.2 ± 19.7</td>
<td>78.3 ± 17.3</td>
<td>0.04</td>
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<td>Body mass index (kg/m²)</td>
<td>28.9 ± 5.7</td>
<td>26.1 ± 6.4</td>
<td>0.01</td>
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<td>44-h Ambulatory systolic BP (mmHg)</td>
<td>143.9 ± 9.7</td>
<td>145.7 ± 10.1</td>
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<tr>
<td>44-h Ambulatory diastolic BP (mmHg)</td>
<td>83 ± 10.2</td>
<td>82.2 ± 10.1</td>
<td>0.68</td>
</tr>
<tr>
<td>44-h Ambulatory pulse (/min)</td>
<td>78.5 ± 10.7</td>
<td>76.3 ± 10.3</td>
<td>0.23</td>
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Bold fonts indicate variables where there was a significant difference between groups.
baseline in systolic BP for fold change in BNP concentration adjusted for the baseline BNP. The modeled changes are plotted at the log mean BNP at baseline of 92 pg/mL. For no change from baseline (1-fold change), there was a decline seen in the ultrafiltration group at both 4 and 8 weeks. Similar results were evident when there was 0.1-fold change (or 90% reduction from baseline in BNP). Thus, the BNP change was not statistically predictive of change in systolic BP for either group.

Assessment of change from baseline in systolic BP with the change from baseline in BNP independent of group assignment gave similarly negative results (model P = 0.15).

**DISCUSSION**

The major findings of this study are as follows: (i) The magnitude of decline in BNP is dependent on the baseline concentration of BNP, but does not require probing dry weight or weight loss. (ii) There is no relationship between decline in postdialysis weight upon probing dry weight and baseline BNP. Furthermore, upon probing dry weight, reduction in BNP is not required for decline in postdialysis weight. (iii) Pre-dialysis log BNP is modestly predictive of ambulatory BP independently of other risk factors such as age, sex, race, body
mass index, diabetes and smoking. (iv) There is no relationship between decline in BP upon probing dry weight and baseline BNP. Furthermore, upon probing dry weight, reduction in BNP is not required for decline in systolic ambulatory BP. Taken together, these findings suggest that the BNP is not a volume marker among hypertensive patients on hemodialysis.

**FIGURE 3:** (A) Scatter plots and least squares linear regression of log BNP and systolic BP. (A) The relationship between log baseline BNP and 44-h ambulatory systolic BP. Open circles represent the control group and closed circles the ultrafiltration group. The relationship was significant as discussed in the text. (B) Dashed lines represent the regression slope for the control group, and solid lines for the ultrafiltration group. Abscissa shows the log baseline BNP (at week 0) and the ordinate the 44-h ambulatory systolic BP at week 4. The regression relationship of ultrafiltration group is weakened. Panel (C) Abscissa shows the log baseline BNP (at week 0) and the ordinate the 44-h ambulatory systolic BP at Week 8. The regression relationship of the ultrafiltration group is further weakened. (D) Abscissa shows the log BNP at Week 4 and the ordinate the 44-h ambulatory systolic BP at Week 4. Regression relationships remain significant. (E) Abscissa shows the log BNP at Week 8 and the ordinate the 44-h ambulatory systolic BP at Week 8. Regression relationship for the ultrafiltration group is now flat and insignificant.

**FIGURE 4:** (A) Time trend of change from baseline (week 0) in 44-h interdialytic ambulatory systolic BP. Light gray bars represent the control group and darker bars the ultrafiltration group. Error bars represent 95% confidence intervals. A significant change from baseline is noted in ambulatory systolic BP, the magnitude of which is not related to the baseline BNP concentration. (B) Time trends of change from baseline in 44-h interdialytic ambulatory systolic BP and the change from baseline in predialysis BNP concentrations. No significant relationship was noted between change from baseline in BNP and change from baseline in systolic BP.

**Time trends in change in BNP**

The time trend of log BNP was strong and significant. Moreover, it was independent of both weight loss and assignment to the ultrafiltration group. Thus, neither weight loss nor ultrafiltration is necessary for reduction in BNP concentration. A higher BNP level was associated with a greater decline in BNP suggesting regression to the mean.
In an observational study, Lauster et al. reported that among 21 patients with elevated post-hemodialysis cGMP levels (>20 pmol/mL), dry weight was probed; weight reduction was associated with a decrease in cGMP levels in all cases and with a decrease in ANP in all but two cases [10]. A control group was not used. Our study also found that BNP declined over weeks, but the control groups had a much greater difference with subjects who had their dry weight probed. While it is possible that as yet unknown factors modulate BNP levels among patients on hemodialysis, it does not appear that volume reduction is predominant among those factors.

**BNP as a predictor of postdialysis weight change on probing dry weight**

If the BNP is a marker of volume among dialysis patients, then greater weight loss should be possible upon probing dry weight among those with elevated BNP concentrations. Baseline BNP was not predictive of weight loss in either the control group or the ultrafiltration group. Furthermore, a change from baseline in BNP concentration was also predictive of weight loss. The only longitudinal study, discussed above, did not have a control group; therefore, our results modify the conclusions of the earlier study [10].

**Relationship of BNP with ambulatory BP**

Log BNP was modestly and independently related to systolic 44-h ambulatory BP. When dry weight was not changed (control group), BNP was even more strongly related to BP 8 weeks later. However, when dry weight was reduced, this lagged relationship was completely thwarted.

We have previously reported an independent relationship among hemodialysis patients of log NT-pro BNP and home systolic BP [7]. BNP is strongly related to the left ventricular mass index [12, 13]. The left ventricular mass index is also related to arterial stiffness [26]. Since the log BNP was independently related to pulse pressure, a proxy for arterial stiffness, and remained significantly related even after adjustment for systolic BP, it is consistent with the hypothesis that the relationship of BNP with systolic BP is not due to volume but arterial stiffness.

**BNP as a predictor of BP response to probing dry weight**

Pre-dialysis BNP concentration at baseline was not a predictor of BP response upon probing dry weight. Time-dependent BNP concentration changes were similarly uninformative of declines in systolic ambulatory BP. If we accept the notion that the BNP is a marker of arterial stiffness and not volume, it is possible to explain why removing volume in the ultrafiltration group results in a drop in BP without the requirement of a drop in BNP.

There are limitations of this study. We did not study cGMP or other cardiac natriuretic peptides. Whether similar relationships will hold for other peptides is unclear. The duration of investigation was limited to 8 weeks; whether the results will be different if the study was extended to 6 months or 1 year is unclear. The strengths of this study include the first assessment of the value of BNP in a randomized investigation with a prespecified hypothesis. Although the number of patients was small, it is still the largest study to date evaluating the role of BNP in long-term hemodialysis patients as a marker of volume.

In summary, BNP neither predicts the ability to reduce weight, nor the response to BP upon probing dry weight. Although BNP may be related to excess arterial stiffness, the results of this investigation suggest the limited value of this cardiac natriuretic peptide in the assessment of dry weight. Taken together, these data suggest that among patients on long-term hemodialysis with hypertension, BNP is a poor marker of volume excess. Therefore, BNP levels should not be used in the determination of dry weight [27].

**ACKNOWLEDGEMENTS**

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**CONFLICT OF INTEREST STATEMENT**

R.A. is a consultant to Roche, Merck, Takeda, Daiichi Sankyo, Sigma Tau, serves on the speaker bureau of Merck and Abbott, steering committees of Abbott and Reata and has received research support from NIH, VA and Daiichi Sankyo.

**REFERENCES**


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