A Cut off Value for Brain Natriuretic Peptide Indicating Volume Overload in Hemodialysis Patients

Aber Halim Baki1*, Amr Mohab1, Cherry Reda1 and Ayman Morttada2
1Department of Nephrology, Ain Shams University, Cairo, Egypt
2Department of Cardiology, Ain Shams University, Cairo, Egypt

Abstract

Introduction: Accurate volume status evaluation leads to better control of hypertension and blood pressure in Hemodialysis (HD) patients. Unfortunately, there is a lack of a reliable objective tool that can be used to measure volume status in daily clinical practice. Brain Natriuretic Peptide (BNP) is an important biomarker in patients with Chronic Kidney Disease (CKD). Whether it is a predictor of weight change or Blood Pressure (BP) response upon probing dry weight among hemodialysis patients remains unknown with lack of standardized cut-off values in HD patients.

Aim: To find a cut-off value for BNP in HD patients with fair cardiac function which indicates concealed volume overload, to preserve cardiac function and reduce the risk of cardiovascular mortality on the long term.

Method: 40 End-Stage Renal Disease (ESRD) patients on regular hemodialysis 3 times weekly were enrolled.

Inclusion criteria: (1) Ejection fraction >55%, LV end systolic (2-4 cm) and diastolic (3.7-5.5 cm) internal dimensions by echocardiography.

(2) Patients with mild LVH; intraventricular wall thickness in diastole <1.3 cm.

(3) Hypertensive patients; with or without antihypertensive medications.

Exclusion criteria: Patients with volume or pressure overload due to other causes than fluid overload (i.e. anemia, heart failure and aneurysmal dilatation of vascular access).

Laboratory investigations were done with serum BNP samples collected post dialysis. Radiological studies included echocardiography, Inferior vena cava collapsibility index for assessment of volume status.

Results: We found no statistical significant differences between hyper and normovolemic patients as regard patient’s characteristics including gender, smoking and presence of diabetes mellitus or hypertension. Also, no significant correlation was present between BNP and patient’s characteristics (age, gender) or laboratory investigations (S. Creatinine, S. Ca, Hb). However, there was an inverse relationship between BNP and IVC collapsibility index. Patients with hypervolemia had significantly higher BNP levels, as compared to the euvolemic patients, with a significant difference (p value=0.011) with the most relevant level of BNP (17.650 pg/ml) to differentiate hyper/normovolemic patients, with a sensitivity of 71% and a specificity of 77.8%.

Conclusion: Our study would appear to provide direct evidence that plasma BNP levels were correlated to the degree of fluid retention in HD patients indicating that elevated levels of BNP could be regarded as a marker of volume overload in absence of other causes of volume and pressure overload (or in absence of heart failure, anemia or vascular access aneurysm).

Keywords: Brain natriuretic peptide; Hypervolaemia; Hemodialysis

Introduction

There is a lack of a reliable biomarker of euvolemia in hemodialysis patients; most physicians rely on clinical criteria to assess patient's volume state [1]. The combination of clinical, biochemical and other measures as inferior vena cava collapsibility rather than depending on a single method is important for proper assessment of the fluid status in such patients [2]. High plasma BNP concentrations in HD patients were associated with volume overload, left ventricular hypertrophy, cardiovascular disease and DM [3]. There is no set cut-off point for either BNP or NT-proBNP for predicting death and cardiac hospitalization in renal patients, but abnormally high levels should signal the need to optimize medical management and to monitor more closely [4].

Aim

The aim of this work is to find a cut-off value for BNP in hemodialysis patients with fair cardiac function which indicates concealed volume overload that need revision of post-dialysis dry weight to preserve cardiac function & reduce the risk of cardiovascular mortality on the long term.

Subjects and Methods

This study has been done on forty patients attending the dialysis center of "Sohag General Hospital" in Sohag, upper Egypt from June 2014 to July 2014, dialyzed 3 times per week.

Inclusion criteria

(a) Normal left ventricular (LV) ejection fraction (>55%), LV

*Corresponding author: Aber Halim Baki, Ain Shams University, 11566, Cairo, Egypt. Tel: 20 2 26831474; E-mail: aberhalim@hotmail.com

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end systolic (2-4 cm) and diastolic internal (3.7-5.5 cm) diameters by echocardiography.

(b) Patients with mild LVH; intraventricular wall thickness in diastole<13 mm.

(c) Patients with hypertension with or without antihypertensive medications.

Exclusion criteria

Patients with volume or pressure overload due to other causes than fluid overload.

(a) Patients with congestive heart failure.

(b) Patients with significant structural valve lesion, LV dysfunctions on echocardiography.

(c) Patients with hyper-dynamic circulation e.g. anemia

(d) Patients with aneuysmal dilatation of AV vascular access.

(e) Patients with pulmonary hypertension.

All patients had: Full history taking with special emphasis on age, gender, diabetes mellitus, hypertension, pre-existing chronic disease affecting other systems e.g. COPD, the cause of end stage kidney disease & co-morbid conditions. Clinical examination including blood pressure, pulse, temperature, cardiac examination, signs of other system affecion, signs of volume overload e.g. lower limb edema, body mass index and post-dialysis BP.

Pre-dialysis sample was taken for chemistry analysis; complete blood picture, serum creatinine, urea and uric acid, serum ALT, AST, bilirubin, albumin, serum Na, K and calcium with post-dialysis sampling for BNP. Serum BNP level was analyzed using serum separator tube and allow sample to clot for 30 minutes before centrifugation for 20 minutes then remove serum and store samples at -20 c. The samples have been collected post dialysis.

Echocardiography: Including assessment of LV dimensions and function, any valvular affecion and IVC collapsibility index. Echocardiography of the IVC can easily be done by a transthoracic, subcostal approach, the transducer position is just below the xiphisternum 1-2 cms to the right of the midline with the marker dot pointing towards the sternal notch. The IVC collapsibility index is expressed as the difference between the value of the maximum diameter (on expiration) and the minimum diameter (on inspiration), divided by the maximum of the two values

\[\frac{(IVC_{max}-IVC_{min})}{IVC_{max}}\times 100.\]

Volume status was classified as Hypervolemia, IVCCI <40% and hypovolemia, IVCCI >75% and values between these extremes were considered to indicate normovolemia [5].

Statistical analysis of the data was done and statistical package for social sciences (IBM-SPSS) version 22 IBM- Chicago, USA was used for statistical data analysis. Data expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as descriptive value for quantitative data. Student t-test was used to compare the means between two groups, and one-way analysis of variance (ANOVA) test was used to compare means of more than two groups. Pearson correlation test was used to compare two quantitative variables. For all these tests, the level of significance (P-value) can be explained as:

No significance P>0.05, Significance P<0.05 and High significance P<0.001.

Results

Our study included forty patients with end stage kidney disease under maintenance regular hemodialysis. Twenty six patients (65%) were males whereas fourteen patients (35%) were females (Table 1), with a mean age of 33.18 ± 12.32 years (Table 2) and the mean body mass index of our patients in this study was (25.77 ± 2.57) Kg/m² (Table 2). Also, the mean duration of dialysis of the Patients was (24.85 ± 21.52) months (Table 2). In this study, end-stage kidney disease was attributed to hypertensive nephropathy (25%), chronic pyelonephritis (20%), renal calculus disease (20%), diabetic nephropathy (15%), chronic glomerulonephritis (10%) and to other miscellaneous causes in (10%) (Figure 1).

The mean post dialysis systolic blood pressure was 140.38 ± 26.224 mmHg and the mean post dialysis diastolic blood pressure was 81 ± 13.737 mmHg (Table 2). Seven cases out of 40 cases were known to be diabetic and 19 cases out of 40 cases were hypertensive (long standing).

Table 1: Demographic features of the study group.

<table>
<thead>
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<th>Parameters</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td></td>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td>DM</td>
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</tr>
<tr>
<td></td>
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<tr>
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<td></td>
<td>NO</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>NO</td>
<td>23</td>
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Table 2: Clinical parameters of the studied group.

<table>
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<th>SD</th>
<th>Min</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.17</td>
<td>12.32</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.77</td>
<td>2.57</td>
<td>21.5</td>
<td>30.5</td>
</tr>
<tr>
<td>Dialysis duration (months)</td>
<td>24.85</td>
<td>21.52</td>
<td>4</td>
<td>108</td>
</tr>
<tr>
<td>Post dialysis SBP (mmHg)</td>
<td>140.38</td>
<td>26.22</td>
<td>90</td>
<td>180</td>
</tr>
<tr>
<td>Post dialysis DBP (mmHg)</td>
<td>81.00</td>
<td>13.73</td>
<td>55</td>
<td>110</td>
</tr>
</tbody>
</table>
Regarding special habits, 17 patients were smokers (42.5%). Regarding the laboratory results, Table 3 shows that the mean serum Hemoglobin (Hb) level was 11.2 ± 0.76 g/dl and the mean hematocrit level was 40 ± 3.5%, the mean serum albumin level was 3.76 ± 0.57 g/dl, the mean serum creatinine level was 8.0 ± 3.22 mg/dl, the mean serum urea level was 115 ± 25.05 mg/dl and the mean serum sodium level was 144.07 ± 2.30 mmol/L, also the mean serum potassium was 4.93 ± 0.87 mmol/L, while mean serum calcium level was 7.84 ± 0.67 mg/dl (Table 3). The mean collapsibility index in the patients of this study was 29.24 ± 14.37% (Table 3). Most of our patients were hypervolemic 31 patients (77.5%) vs. 9 patients (22.5%) normovolemic (Table 4). There was no significant difference between hypervolemic and normovolemic patients regarding patient’s characteristics including gender, smoking, DM and hypertension (Table 5).

Table 6 shows that there was no significant difference between hypervolemic and normovolemic patients regarding age, body mass index and dialysis duration. There was no significant difference between hypervolemic and normovolemic patients as regard laboratory investigations including serum creatinine, urea, albumin, Na, Ca and hematocrit value (Table 6). There was a no significant correlation between serum BNP level and patient’s characteristics including age, body mass index and duration of hemodialysis (Tables 7 and 8).

There were no significant correlations between serum BNP level and any of the routine laboratory investigations (Table 9). There was a negative and significant correlation between BNP and collapsibility index of the inferior vena cava, which means that there is an inverse relationship between them (Table 10 and Figure 2). ROC analysis shows that BNP can differentiate patients with hypervolemia from those with or without a significant difference (p value=0.011) (Table 10).
and Figure 3). Using coordinate points of the above ROC curve, the most relevant level of BNP is 17.65 pg/ml to differentiate hypervolemic from normo or hypovolemic patients with a sensitivity of 71% and a specificity of 77.8% (Table 11).

**Discussion**

The search for biomarkers for detection of hypervolemia among hemodialysis patients is of particular importance because occult volume overload is common and accounts for a large burden of volume-related hospitalizations [6]. The biologically active form of BNP and the inactive amino terminal fragment NT-proBNP represent cleavage products of the precursor pre-pro BNP which is synthesized by ventricular myocytes in response to physiological signals such as stretching of the ventricular wall, changes in systemic blood pressure, sodium levels or extracellular volume [7]. High plasma BNP concentrations in HD patients were associated with volume overload, left ventricular hypertrophy, cardiovascular disease and DM. Plasma BNP concentration may be a useful parameter for assessing the risk of cardiac death in HD patients by providing prognostic information independently of other variables previously reported [3]. In this study we tried to find out a cut off value for BNP in hemodialysis patients with fair cardiac function which indicates concealed volume overload that

<table>
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<th>Male</th>
<th>Female</th>
<th>T test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml)</td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>22.04</td>
<td>9.09</td>
<td>24.55</td>
<td>13.30</td>
</tr>
<tr>
<td>Smokers</td>
<td>Non smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>24.65</td>
<td>11.04</td>
<td>21.64</td>
<td>10.41</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Non-Diabetic</td>
<td></td>
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<tr>
<td>BNP (pg/ml)</td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>25.40</td>
<td>15.79</td>
<td>22.39</td>
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<td>Non-Hypertensive</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>22.45</td>
<td>12.43</td>
<td>23.34</td>
<td>9.04</td>
</tr>
</tbody>
</table>

Table 7: Correlation between serum BNP level and patients' characteristics of the study group.

![Figure 2](image1.png)  
**Figure 2:** Correlation between BNP and collapsibility index of the inferior vena cava.

![Figure 3](image2.png)  
**Figure 3:** ROC curve analysis for BNP level (taking collapsibility index of the inferior vena cava as a gold standard for diagnosis of hypervolemia).
need revision of post-dialysis dry weight to preserve cardiac function and reduce the risk of cardiovascular mortality on the long term.

Ghaffari reported that collapsibility index of inferior vena cava in the patients without clinical edema was higher compared to patients with mild and significant edema [8]. In this study there was no significant difference between hypervolemic and normovolemic patients as regard patient’s characteristics including gender, smoking and presence of DM or hypertension. These results agreed with Khalaj et al. who reported that there was no correlation between the intra-dialytic changes in plasma volume or body weight and pre and post-dialysis SBP or DBP. He explained that these results may be attributed to strict exclusion criteria of his study which finally led to selection of patients with high re-filling rate of plasma volume (non-diabetic and appropriate cardiac function) [9]. In contrast to our results Santos et al. reported that volume expansion is perhaps the major factor in the development of hypertension in dialyzed patients. It leads to an elevation in BP via the combination of a rise in cardiac output and an inappropriately high systemic vascular resistance [10]. Also in contrast to our results Lins et al. reported a positive correlation between SBP alteration and plasma volume change [11]. Furthermore, the HEMO study revealed that interdialytic weight gain correlated to high pre-dialysis blood pressure [12]. Concerning laboratory investigations as serum creatinine, urea, uric acid, serum albumin, sodium, potassium and calcium levels, no statistically significant difference was found between hypervolemic and normovolemic dialysis patients. In contrast, Antlanger et al. reported that fluid overload is most common in hemodialysis patients with low body mass index and lower serum albumin levels but similar to our results; there was no significant difference between hypervolemic and normovolemic patients regarding gender and age [13].

Our results showed statistically significant increase in serum BNP level in hypervolemic dialysis patients compared to normovolemic dialysis patients using collapsibility index of inferior vena cava. These results agreed with Naganuma et al. who reported that high plasma BNP concentrations in HD patients were associated with volume overload [3]. Also Nishikimi et al. concluded that plasma BNP levels were closely associated with the amount of extracellular water and the overhydration status in hemodialysis patients [14]. On the other hand, Osajima et al. found no significant correlation between changes in plasma BNP concentration and reductions in body weight during HD [15]. Also, Cataliotti et al. reported that BNP concentrations in HD patients without cardiovascular anomalies, hypertensive heart disease or ventricular dysfunction did not differ from those obtained from healthy subjects without cardiovascular or renal pathology [16].

In our study, there was no significant correlation between serum BNP level and patient’s characteristics including gender, smoking or age which was in agreement with Frankenstei et al. who found no relation between high levels of BNP and NT-proBNP with increased age or specific sex [17]. Also Bavbek et al. reported that there was no significant correlation found between plasma BNP levels and clinical parameters such as duration of dialysis, systolic and diastolic blood pressures or serum urea, creatinine, calcium, and phosphorus levels, mean BNP levels are generally increased in dialysis patients compared to the traditional cut-off levels [18]. On the other hand, Tagore et al. found that age was correlated with BNP levels in univariate analysis but inherently provided no predictive value [19]. According to our results there is no significant correlation between BNP level and body mass index which disagreed with Wiley et al. who reported that there is a significant correlation between BNP and body mass index [20]. In this study, there was no significant relation between BNP level and duration of hemodialysis which was in agreement with Halal et al. who concluded that there was no relation between mean BNP level and total period in dialysis [21].

However, Bednarek-Skublew ska, et al. reported direct association between increased serum BNP level and longer total duration of HD [22]. In this study there was no significant correlation between BNP levels and presence of hypertension or presence of diabetes. These results agreed with Sheen, et al. [23], who reported that the correlation of BNP changes, whether intra or inter-dialytic did not correlate with changes in weight, systolic and diastolic blood pressure. These results were attributed to several possibilities which may explain this negative finding. The first is that changes in BNP may be related to the dialysis procedure itself as opposed to changes in volume status. It is doubtful that BNP is removed across the dialyzer, but cytokine changes during dialysis may alter the extra-renal clearance of BNP during dialysis. The second is that post-BNP levels were sampled immediately after the end of the session and thus, adequate time for achieving a steady state of intravascular volume had not yet been established. Our results showed inverse significant correlation between serum BNP level and collapsibility index of inferior vena cava. Basso, et al. [24] reported that there was a significant reduction in collapsibility index of inferior vena cava and BNP after HD (p<0.001), these results was attributed to that the re-equilibration of interstitial and intravascular compartments after HD takes some time and the optimal timing for post-HD assessment is not clear.

The ROC curve analysis showing that BNP can differentiate between patients with hypervolemia from those with or without a significant difference (p value<0.011). Using coordinate points of the ROC curve, the most relevant cut off level of BNP was 17.65 pg/ml to differentiate hypervolemia from normo or hypovolemic patients with a sensitivity of 71% and a specificity of 77.8%. Unfortunately, there was lack of studies that compared collapsibility index of inferior vena cava as a gold standard for detecting hypervolemia in hemodialysis patients and plasma levels of BNP to detect a specific cut off value of it.

Conclusion
Plasma BNP levels are to be correlated to the degree of fluid retention in HD patient. Thus, elevated levels of BNP should be regarded as markers of increased volume overload.

Recommendations
(a) Serum BNP level is a reliable volume marker to assess volume overload so should be included in routine investigations of hemodialysis patients.
(b) There is a need to conduct other large studies.
(c) Further development of the methods for actual measurement of volume status in dialysis patients is necessary for attaining an easily derived and utilized index for adequacy of fluid removal.
(d) According to methods we should measure both BNP and BP before and after dialysis.
(e) We recommend undergoing studies that compare between levels of BNP in hemodialysis patients with structural heart disease and patients with fair cardiac function.

References


