Fluid overload correction and cardiac history influence brain natriuretic peptide evolution in incident haemodialysis patients

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Abstract

Objectives. Brain natriuretic peptide (BNP) is a cardiac peptide secreted by ventricle myocardial cells under stretch constraint. Increased BNP has been shown associated with increased mortality in end-stage renal disease patients. In patients starting haemodialysis (HD), both fluid overload and cardiac history are frequently present and may be responsible for a high BNP plasma level. We report in this study the evolution of BNP levels in incident HD patients, its relationship with fluid removal and cardiac history as well as its prognostic value.

Methods. Forty-six patients (female/male: 21/25; 68.6 ± 14.5 years old) surviving at least 6 months after HD treatment onset were retrospectively analysed. Plasma BNP (Chemoluminescent Microparticule ImmunoAssay on i8200 Architect Abbott®, Paris, France; normal value < 100 pg/mL) was assessed at HD start and during the second quarter of HD treatment (Q2).

Results. At dialysis start, the plasma BNP level was 1041 ± 1178 pg/mL (range: 14–4181 pg/mL). It was correlated with age (P = 0.0017) and was significantly higher in males (P = 0.0017) and in patients with cardiac disease history (P = 0.001). The plasma BNP level at baseline was not related to the mortality risk. At Q2, predialysis systolic blood pressure (BP) decreased from 140.5 ± 24.5 to 129.4 ± 20.6 mmHg (P = 0.0001) and the postdialysis body weight by 7.6 ± 8.4% (P < 0.0001). The BNP level decreased to 631 ± 707 pg/mL (P = 0.01) at Q2. Its variation was significantly correlated with systolic BP decrease (P = 0.006). A high BNP level was found associated with an increased risk of mortality.

Conclusions. Hence, plasma BNP levels decreased during the first months of HD treatment during the dry weight quest. Whereas initial BNP values were not associated with increased mortality risk, the BNP level at Q2 was independently predictive of mortality. Hence, BNP is a useful tool to follow patient dehydration after dialysis start. Initial fluid overload may act as a confounding factor for its value as a prognostic marker because of cardiac disease.

Keywords: brain natriuretic peptide; cardiac disease; haemodialysis; incident patients; systolic blood pressure

Introduction

Extracellular fluid overload and its haemodynamic consequences are a usual complication reported in end-stage renal disease (ESRD) patients [1]. It is associated with the high frequency of arterial hypertension at dialysis start. Removing fluid, i.e. the dry weight quest, after dialysis initiation corrects hypertension [2]. However, we lack the tools to follow that quest. Among the available markers, brain natriuretic peptide (BNP) has been shown to be associated with fluid excess [3, 4]. It is a cardiac peptide secreted by ventricle myocardial cells under stretch constraint. Increased BNP has been shown to be associated with left ventricular hypertrophy, cardiac dysfunction [5] and increased mortality [6] in prevalent ESRD patients. The relationship between extracellular fluid handling and the BNP variation has not been reported yet in incident haemodialysis (HD) patients. The purpose of this study is to check the baseline BNP level when ESRD patients start HD therapy and its evolution during the first months of
dialysis therapy. The rationale is to define BNP as a tool to assess fluid removal in this setting and to analyse its relationship as a prognostic factor.

Patients and methods

Since November 2006, the BNP level is assessed during the first week of HD treatment and then every quarter from predialysis blood drawing at the midweek session. All incident patients between November 2006 and August 2008 who were assessed for BNP level (Chemiluminescent Microparticule ImmunoAssay on i8200 Architect Abbott®, Paris, France; normal value <100 pg/mL) during the first week of dialysis start and during the second quarter (Q2) were included in this study. When BNP was assessed several times during these periods, the average of the BNP values was used. All incident patients were evaluated at baseline from the chart for cardiac disease, present in 17 patients: coronary artery disease (nine cases), arrhythmia (seven cases) and dilated cardiomyopathy (nine cases). The baseline predialysis blood pressure (BP) level was the average of all the predialysis BP data during the first month of HD treatment. Predialysis BP components were compared between the first month (M1) and the Q2 averages. The baseline body weight was the predialysis body weight recorded at the first dialysis treatment. Thereafter, the post-dialysis body weight was averaged on a quarterly basis. The body weight evolution was calculated as a percentage of the ratio between the baseline body weight and the average postdialysis body weight at Q2. Residual renal function at Q2 was estimated upon loop diuretic prescription.

The statistical analysis used average values ± SD. The distribution of BNP level at baseline and Q2 was analyzed using chi-square test. Paired t-test was used to compare BNP, body weight and BP data between dialysis start and the Q2. Correlation between BNP and other parameters was assessed using Spearman rank test because of abnormality of the data distribution. The patients were divided into subgroups according to median of BNP level at start and at Q2. Survival was studied using Kaplan–Meier analysis and log-rank calculation, and multivariate Cox proportional hazard model was applied to test the independence of BNP as a mortality-related factor.

Results

Sixty-four patients started HD treatment during this 22-month period. Excluding patients presenting with premature deaths or missing data, 46 patients remained for analysis. Patient characteristics are displayed in Table 1. The patients’ dialysis prescriptions were as follows: three sessions per week, prescribed treatment time: 5.8 ± 1.1 h per session (5–8 h), prescribed blood flow: 250–300 cc/min and low-flux Helixone® membrane. The average follow-up was 17.2 ± 5.8 months (range: 6.2–28.3 months). During the period, 11 patients died (6 of cardiovascular origin), 1 patient was transferred to another centre and 3 received a kidney graft. Thirty-one patients remained present and alive at the end of follow-up (31 August 2008).

The initial BNP value was 1041 ± 1178 pg/mL (range: 14–4181 pg/mL). The BNP level was higher in patients with cardiac disease history (1934 ± 1291 versus 609 ± 843 pg/mL, P = 0.0001). The BNP distribution at baseline in patients without and with cardiac disease history is displayed in Figure 1. In patients without cardiac disease history, the BNP level was found to be <100 pg/mL in 32%, >1000 pg/mL in 16 and 52% in the 100–1000 pg/mL range. No patients with cardiac disease history were found in the normal range and 73% were found to be >1000 pg/mL. The plasma BNP level was correlated with age (P = 0.0017; Figure 2 and 3) and was significantly higher in males (P = 0.0017) but not different in diabetic patients. In a multiple regression model, the plasma BNP level was significantly associated with age, gender and history of cardiac disease. There was no statistical difference in mortality risk in patients below or above the median of baseline plasma BNP (log-rank test: nonsignificant).

Between baseline and the second quarter of HD treatment, predialysis systolic BP decreased from 140.5 ± 24.5 to 129.4 ± 20.6 mmHg (P = 0.0001). The postdialysis body weight decreased by 7.6 ± 8.4% during this period (P < 0.0001). The average BNP level decreased from 1041 ± 1178 to 631 ± 707 pg/mL (P = 0.015; Figure 4) at Q2. In patients without cardiac disease history, the proportion of patients with plasma BNP level <500 pg/mL increased from 58.1 to 74.2% (P = 0.009), whereas in patients with cardiac disease history, the proportion of patients with plasma BNP level >1000 pg/mL decreased from 73.3 to 53.3% without reaching significance. The duration of the session did not influence the BNP decrease. At Q2, only six patients remained with significant residual diuresis. The BNP level at Q2 was higher in these six patients than in the other patients (1111 ± 791 versus 559 ± 675 pg/mL) but it did not reach significance. There was no significant relationship between the variations of BNP and postdialysis body weight. Using Spearman rank test, the BNP variation (in percentage) between HD onset and Q2 was significantly correlated with systolic (P = 0.006) and diastolic (P = 0.035) BP variations (in percentage). In patients with the average systolic BP >140 mmHg at M1, the systolic BP significantly decreased from 157 ± 11 to 138 ± 15 mmHg (P < 0.0001) with a −8.7 ± 9.0% body weight decrease (P = 0.0005), and the plasma BNP level dropped significantly from 987 ± 1110 to 482 ± 454 pg/mL at Q2 (P = 0.026; Figure 5). In patients with cardiac disease history, the plasma BNP level decreased from 1934 ± 1290 at baseline to 1203 ± 841 pg/mL at Q2 but this decrease did not reach significance such as for the predialysis systolic BP decrease (from 128 ± 26 at M1 to 121 ± 22 mmHg at Q2), despite a significant decrease of post-dialysis body weight (9.1 ± 6.8%, P = 0.0002).

An increased mortality risk was found in the whole group of patients with plasma BNP level at Q2 above the median (median = 350.5 pg/mL; P = 0.015; Figure 6). When included in the multivariate Cox proportional hazard model with other variables such as age, gender, serum albumin and the presence of diabetes, the plasma BNP at Q2 was independently associated with the mortality risk (P = 0.0003). Survival in patients with cardiac disease was better in the subgroup with the higher BNP decrease (in percentage) between baseline and Q2 (Figure 7; P = 0.034). No relationship was found between the BNP levels or decrease and cardiovascular mortality.

Table 1

| Patient characteristics at baseline (HD start) and at the second quarter |
|---------------------------|---------------------|
| Age (years)               | 68.6 ± 14.5         |
| Gender (female/male)      | 21/25               |
| Diabetes                  | 21/46 (46%)         |
| Cardiac disease history   | 18/46 (39%)         |
| Initial BNP (pg/mL)       | 1041 ± 1178         |
| BNP at second quarter (pg/mL) | 631 ± 707     |

Studied patients 46

(continued)
This study brings three types of information regarding the value of plasma BNP in incident HD patients. First, and for the first time, it shows a wide distribution of plasma BNP in ESRD patients starting the HD treatment. In patients without cardiac disease history, 32% of the patients had a normal (<100 pg/mL) plasma BNP level. In prevalent patients, we have reported the same proportion of patients with a normal BNP level [7]. It then appears that severely impaired renal function does not modify importantly the BNP level, opposite to what is reported with the N Terminal-proBrain Natriuretic Peptide [8]. Cataliotti et al. [9] have clearly demonstrated that dialysis patients without left ventricular hypertrophy or cardiac disease have BNP levels similar to control subjects. Even if patients presenting with loss of renal function have increasing plasma BNP levels [10], this finding may be attributed to cardiac consequences of CKD rather than to the renal impairment itself. Essig et al. [11] have shown with bioimpedance (BIA) and echocardiography that cardiac remodelling secondary to extracellular fluid excess occurs at early stages of chronic kidney disease (Stages 1–3). It is not then surprising that a large proportion of patients unknown for cardiac disease had increased value of BNP. On the contrary, and as expected, patients with cardiac disease history had higher BNP levels, with no patients with a normal BNP level and a great majority (73%) with high levels, >1000 pg/mL.

Second, we have observed a significant decrease in plasma BNP level after 3 months of HD treatment in incident dialysis patients. The BNP is a molecule of 32 amino acids, 3.5 kDa of molecular weight with a 15–20 min half-life [12]. The plasma BNP level has been found to be reduced during the dialysis session with low-flux membranes by 18.5% and some BNP was found in the dialysate [13]. However, because of the short half-life of the molecule and the low influence of renal function on its level, it is expected that the predialysis level of BNP reflects the cardiac constraint by fluid and/or heart disease. In our opinion, applying the dry weight method as described by Charra et al. [14] relieves the fluid overload cardiac consequences and significantly decreases the BNP levels. As the method is universally applied to our patients, whatever the length of the session, it may explain why treatment time had no influence on BNP decrease. Fluid removal is attested by the weight decrease. The concomitant BP decrease is expected according to our experience [2] and from a recent controlled study by Agarwal et al. [15]. The BNP level reduction was found to be statistically associated to the BP decrease. The effect of fluid excess on BNP levels has been reported by Fagugli et al. [4], who found a significant relationship between the amount of extracellular water measured from BIA and the plasma BNP level. Also, a significant relationship between predialysis BNP level and the extracellular water/total body water ratio assessed from BIA has been shown by Lee et al. [16]. However, there are large interplays between fluid removal and improvement of cardiac function that may influence BNP production and reduction. Toz et al. [17] have shown a spectacular improvement of ejection fraction with long and slow ultrafiltration. Also, short daily HD, independent of the body weight variation, may improve cardiac dysfunction and BNP reduction by reducing the effect of the interdialytic weight gain [18]. Hence, during the dry weight quest, assessing the plasma BNP level may help to follow the patient dehydration. If a patient with no cardiac disease
history presents with a high BNP level, the progressive decrease of the postdialysis body weight may be prescribed. However, it is difficult to anticipate the individual target level. In the absence of severe cardiac disease, such as dilated cardiomyopathy or coronary heart disease, left ventricular hypertrophy itself may trigger a high plasma BNP level [5]. Lee et al. [16] have underlined the absence of a relationship between the predialysis BNP level and the states of normo- or under-hydration. Our data from patients with cardiac disease did not find a comparable significant decrease of BNP values with fluid removal, and some patients may remain with a high BNP level even after sustained fluid removal because of the cardiac status. Also, in the absence of body composition analysis, the possibility that the BNP decrease might occur without intervention postdialysis cannot be ruled out, for instance because of cardiac improvement after dialysis start. However, fluid removal seems to be important in heart failure, as suggested by Toz et al. [17]. Also, uraemia correction after starting dialysis may restore appetite and anabolism. Spontaneous and progressive changes in body composition (more lean and/or fat mass, less extracellular fluid) might happen leading to BNP level decrease [2].

Third, our findings regarding the relationship between plasma BNP level and mortality risk deserve interpretation. At baseline, a high BNP level was not clearly associated with an increased mortality risk. It is the opposite to what was reported by Zoccali et al. [5]. But this last large study included a prevalent cohort of HD patients. From our data, after several months of HD treatment, the BNP decreased significantly, especially in hypertensive patients, and the relationship between high levels of plasma BNP and the increased risk of mortality was significant. The multivariate analysis confirmed that a high BNP value after several months of HD treatment was associated with an increased mortality risk. Hence, it seems that the relationship between BNP level and mortality changes over time. In our opinion, besides the cardiac status itself, fluid overload influences also the BNP level, acting as confounding factor.
Correcting the fluid overload during the first months of HD treatment restores the prognostic value of BNP as a cardiac prognosis marker. The fact that the BNP decrease after the dry weight quest did not reach significance in patients with cardiac disease supports this hypothesis. In these patients, and because of the small number, the association between the BNP decrease and the better survival remains to be confirmed. It would highlight the important prognosis value of BNP in these patients.

Our study has several important limitations. It included a limited number of patients. Applicability will have to be verified in a more important cohort, especially to assess the relationship between the BNP levels at different times and the BNP variation after dialysis start. However, the fact that it is an incident cohort after standard follow-up during CKD evolution and on which is applied a uniform policy for hyperhydration fluid excess correction make, in our opinion, these results highly reproducible. Also, the definition of cardiac disease relied only on chart analysis. However, the clear differences that were found between patients with and without cardiac disease demonstrate that the retrieved information was appropriate. Adding echocardiography data would be really informative, especially to identify patients with left ventricular hypertrophy. This would allow a better classification of the patients and explain why some patients without cardiac history may present with high BNP values. However, it would not change the advice that a patient with a high BNP level requires fluid withdrawal. Using measurement of BIA combined with BNP assessment deserves to be studied because combining precise extracellular fluid measurement as provided by new BIA generation device [19, 20] and BNP assessing the cardiac consequences may improve patient care. Moreover, the blood access flow was not included in the study, whereas it can influence the BNP level [21].

In conclusion, in incident ESRD patients starting the HD treatment, a significant proportion of patients have a high plasma BNP level that may be influenced both by cardiac disease history and fluid overload. The correction of fluid excess improves both the BP level and the BNP level, especially in dialysis patients without cardiac disease history. Sequential assessment of predialysis plasma BNP level may help the clinician in the correction of extracellular fluid excess to follow the improvement of the cardiac status and improve long-term patient outcomes.

Conflict of interest statement. This study has been has been presented and published in abstract form at the International Society of Blood Purification meeting in Stockholm, September 2009.

References


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