Original Paper

N-Terminal Prohormone of Brain Natriuretic Peptide but not C-Terminal Pre-Pro Vasopressin (Copeptin) Level is Associated with the Response to Antihypertensive Therapy in Haemodialysis Patients

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Key Words

NT-proBNP • Copeptin • Hypertension treatment • Antihypertensives • Haemodialysis

Abstract

Background/Aims: Volume overload, frequently clinically asymptomatic is considered as a causative factor limiting the effectiveness of antihypertensive therapy in haemodialysis (HD) patients. Therefore, the aim of this study was to assess plasma levels of N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and a C-terminal portion of the precursor of vasopressin (CT-proAVP, copeptin), surrogate markers of volume overload in

HD patients in relation to the number of antihypertensive drugs used in the hypertension treatment. **Methods:** One hundred and fifty adult HD patients (92 males) were enrolled into this study. Clinical data concerning blood pressure (BP) measurements prior haemodialysis session and pharmacotherapy were collected from all patients. In addition to routine laboratory parameters, plasma levels of NT-proBNP and CT-proAVP were measured, and daily sodium and water consumption were estimated with a portion-size food frequency questionnaire. **Results:** Among 145 (96.7%) hypertensive HD patients, 131 were receiving antihypertensive medication. Despite antihypertensive therapy, 31.0% had inadequate BP control. Plasma concentration of NT-proBNP was associated with systolic ($R=0.19$; $p=0.02$) but not diastolic BP values and with the number of received antihypertensive drugs ($R=0.21$; $p=0.01$). The highest NT-proBNP values were observed in patients receiving 3 or more antihypertensive drugs. In contrast, no significant correlation was found between plasma CT-proAVP concentrations and BP values as well as and the number of antihypertensive drugs. Receiver operator curve analysis showed that NT-proBNP values over 13,184 pg/mL predicted the use of at least 3 antihypertensive drugs in maximal doses in the therapy of hypertension, similar analyses performed for CT-proAVP showed much less specificity. **Conclusions:** 1. Increased levels of NT-proBNP seems to be a better biomarker of multidrug antihypertensive therapy requirement than CT-proAVP. 2. Whether estimation of NT-proBNP in these patients will be also better biomarker than copeptin in the prediction of cardiovascular complications related to hypertension needs further investigations.

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Introduction

It is estimated that approximately 72-86% patients on haemodialysis (HD) therapy are suffering from hypertension [1-3], that is associated with annual mortality of 23% [4]. According to National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines, blood pressure values below 140/90 mmHg measured immediately before dialysis session are recommended for all dialysis patients [5]. Although, the exact data concerning the proportion of treated hypertensive HD patients who achieve adequate blood pressure control, and the number and structure of antihypertensive drugs used are widely missing in this population. It should be acknowledged that the definition of resistant hypertension in the population of HD patients is not applicable due to the lack of diuretics efficacy in oliguric/anuric patients. Hypertension in HD patients often reflects inadequate volume control [6], and preservation of fluid in the extracellular space [7]. It should be stressed that the clinical assessment of volume overload could raise significant difficulties as up to now, there is the lack of simple reliable, validated, clinically applicable method for volume assessment in HD patients. Different physical examination and findings can be used to diagnose excessive volume overload; among others, the presence of pedal edema, elevated jugular venous pressure, hepatjugular reflex, basilar rales, and the presence of left ventricular fourth heart sounds. The simplest clinical appreciation of signs of volume overload, such as peripheral edema, lacks sensitivity, as it may reflect excess vascular permeability, stasis, or may result from the use of vasodilator drugs including dihydropyridines [8]. More advanced, increasingly utilized, high reproducibility, objective methods to evaluate objectively fluid status include bioimpedance, inferior cava vein (ICV) diameter measurement or lung ultrasonography [9]. Bioimpedance allows quantification of excess extracellular volume by comparison with a healthy population. This safe and noninvasive method can be used to determine hydration status in patients on dialysis therapy, and different from other methods allows the quantification of intracellular and extracellular volumes [6, 10, 11]. However, this approach is time-consuming and difficult to handle in everyday practice. It should be also emphasized that severe obesity, cutaneous alterations, inadequate skin adherence of electrodes, electrical interference or incorrect positioning can limit bioimpedance accuracy. Lung echography, through B-lines score evaluation, detects an excess of extravascular lung water. Ultrasound lung comets (ULC) or

B-lines are defined as multiple comet tails originating from the water-thickened interlobular septa. ULC score is a simple, echographic method for semi-quantitative assessment

Table 1. Demographic and clinical characteristics of 150 haemodialysis patients (mean $\pm$ SD). # mean values from measurements performed before 6 consecutive haemodialysis sessions ^ mean value from last 6 months * percentage of patients with diabetes

Characteristics	
Age (years)	62 $\pm$ 15
Gender (male/female)	92 / 58
Body mass index (kg/m ²)	26.1 $\pm$ 5.2
Obesity (BMI $\geq$ 30 kg/m ²) (n/%)	28 / 18.7
Systolic BP (mmHg)#	132.9 $\pm$ 16.1
Diastolic BP (mmHg)#	75.5 $\pm$ 8.9
Primary cause of CKD (n/%)	
Diabetes	42 / 28.0
Hypertension	17 / 11.3
Nephrolithiasis	8 / 5.3
Autosomal Dominant Polycystic Kidney Disease (ADPKD)	10 / 6.7
Ischemic nephropathy	2 / 1.3
Glomerulonephritis	24 / 16.0
Interstitial nephritis	13 / 8.5
Other or unknown	34 / 22.7
Time on dialysis (months)	48 $\pm$ 48
Kt/V (per HD session)^	1.05 $\pm$ 0.3
Ultrafiltration (L)	2.47 $\pm$ 0.9
Residual diuresis (mL)	452 (374-532)
Co-morbidity (n/%)	
Hypertension	145 / 96.7
Diabetes	55 / 36.7
Coronary artery disease	83 / 55.3
Stroke	12 / 8.0
Past kidney transplantation	11 / 7.3
Antihypertensive pharmacotherapy (n/% of hypertensives)	131 / 90.3
β -adrenolytics (n/% of treated)	99 / 75.6
α -adrenolytics (n/% of treated)	31 / 23.7
Angiotensin converting enzyme inhibitors (n/% of treated)	41 / 31.3
Angiotensin II receptor antagonists (n/% of treated)	8 / 6.1
Calcium channel blockers (n/% of treated)	78 / 59.5
Sympatholytics (n/% of treated)	16 / 12.2
No of antihypertensive drugs (n - in treated patients)	2.1 $\pm$ 1.2
No of antihypertensive drugs corrected for doses (n)	1.6 $\pm$ 1.3
Loop diuretics (n/% of hypertensives)	68 (46.9)
Erythropoiesis stimulating agents – ESA (n/%)	145 (96.7)
Other drugs	
Oral anti-diabetics	19 / 34.5*
Insulin	36 / 65.5*
Antiplatelets	77 / 51.3
Statins	60 / 40.0
Fibrates	0
Oral phosphorous binders	129 / 86.0
Cinacalcet	17 / 11.3
Alfacalcidol	31 / 20.7

extravascular lung water that was shown to predict all-cause mortality, hydration status-mortality and cardiac events in HD patients [12, 13]. However useful, this method is also unable to precisely quantify fluid excess. As the clinical determination of volume state is admittedly difficult, the biochemical markers of hypervolaemia may be useful. N-terminal fragment of the prohormone brain natriuretic peptide

(NT-proBNP) and vasopressin (AVP) are physiological markers of volume overload. Recently, it was shown that a stratification strategy using NT-proBNP and cardiac troponin I (cTnI) values helps to identify HD patients with increased morbidity and mortality due to higher values of systolic blood pressure measured immediately before dialysis session [14]. AVP is an unstable molecule rapidly cleared from plasma and is largely attached to platelets in the circulation. Therefore, most assays have relatively limited reliability. Recently an assay has been developed to measure plasma/serum copeptin, the C-terminal portion of the precursor of AVP (CT-proAVP). The aim of this study was to assess plasma levels of NT-proBNP and CT-proAVP, surrogate markers of volume overload in HD patients in relation to the number of antihypertensive drugs used in the hypertension treatment.

Fig. 1. Flow chart of the study.

Materials and Methods

Study population and data collection

One-hundred and fifty adult HD patients (92 males) were enrolled into this study. Patients were recruited from 10 dialysis centers located in Upper Silesia Region of Poland and underwent haemodialysis (HD) 3 times per week for 3.5–5 h (11.7 ± 0.9 h weekly) using low-flux dialysers with polyethersulphone (PES) or polysulphone (PSU) membranes (area range 1.5–2.0 m²), with blood flow rates from 200 to 250 ml/min and dialysate flow rate 500 ml/min. Patient characteristics including CKD causes, duration of HD therapy and Kt/V are given in Table 1. The flow chart of the study is shown in Figure 1. Patients have been on HD therapy for at least 6 months and gave written consent for participation in this study. Among the exclusion criteria were gastrointestinal tract diseases, current hospitalization, and apparent fluid overload. The study protocol was approved by the Bioethical Committee of the Medical University of Silesia in Katowice (KNW 22/KB1/185/I/11/12).

The study protocol assumed a single withdrawal of an additional blood sample while performing routine tests (blood count, serum urea, calcium, phosphate, sodium, potassium), before the midweek HD session after overnight fasting.

Clinical (including blood pressure - BP measurements prior haemodialysis session) and laboratory data were retrieved from the medical records of dialysis centres. The residual renal function was assessed by residual diuresis reported by patients.

Measurements

Plasma NT-proBNP levels were assessed by electrochemiluminescence method (ECLIA) using commercially available kits on Cobas E411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with inter-assay coefficients of variability below 4.6%.

Plasma CT-proAVP levels were assessed by ELISA using the commercially available kit (Uscn Life Sciences Inc., Wuhan, PRC) with intra-assay and inter-assay coefficients of variability were as follows: < 10% and < 12%, respectively.

Serum hs-CRP was assessed by immunoturbidimetric method (DRG Instruments GmbH for Hybrid XL, Marburg, Germany) with inter-assay precision < 4.8%.

Assessment of diet

To analyze the composition of patient diet during the previous year, a portion-size version of the food frequency questionnaire by the National Institutes of Health - Diet History Questionnaire II (DHQ

Table 2. Biochemical characteristics and the study parameters [(mean & SD or *median (25 – 75 percentile)]. ^ mean value from last 6 months #data for 107 patients

Characteristic	mean&SD
Haemoglobin (g/dL)^	10.8 ± 1.3
Total cholesterol (mg/dL)	169 ± 53
LDL cholesterol (mg/dL)	90 ± 35
HDL cholesterol (mg/dL)	28 ± 9
Triglycerides (mg/dL)	169 ± 108
Calcium (mg/dL)^	5.77 ± 1.13
Phosphorous (mmol/L)^	8.57 (8.44 – 8.70)
Parathyroid hormone (pg/mL)	449 ± 228
Hs-CRP (mg/L)*	4.82 (2.33 – 11.60)
NT-proBNP (pg/mL)*	6424 (2425 – 29306)
CT-proAVP (pg/mL)*	2797 (2073 – 4289)
Water intake (L/day)#	2.16 ± 1.70
Sodium intake (g/day)#	2.86 ± 1.55

Table 3. Mean NT-proBNP, CT-proAVP, residual diuresis, ultrafiltration and sodium intake in normotensive and hypertensive HD patients in accordance with the number of antihypertensive drugs [(mean & 95% CI or *median (25 – 75 percentile)]. #maximal doses, *data for 107 patients, BP - blood pressure

	Normotensives			Hypertensives		
Number of drugs#	0	0	<1	≥1 <2	≥2 <3	≥3
Number of patients	5	14	45	43	24	19
Systolic BP (mmHg)	120.8 (91.8-149.7)	127.5 (116.6-138.3)	131.0 (126.0-135.9)	136.1 (131.3-140.9)	130.3 (124.1-136.6)	140.8 (134.8 – 146.8)
Diastolic BP (mmHg)	77.3 (64.1-90.6)	75.4 (70.7-80.0)	76.1 (73.2 – 78.9)	75.5 (72.6 – 78.5)	73.5 (70.6-76.4)	76.4 (71.7-81.0)
NT-proBNP (pg/mL)*	2132 (2108-22320)	3812 (2425-8436)	5145 (2506-20470)	4684 (2146-30595)	6424 (2037-32205)	19609^^ (7886-35000)
CT-proAVP (pg/mL)*	2812 (2377-8173)	2642 (2166-3512)	2832 (2230-4289)	2935 (2078-4905)	2837 (1916-3829)	2455 (1860-4386)
Residual diuresis (L)	0.15 (0-0.40)	0.45 (0.14-0.76)	0.56 (0.41-0.71)	0.37 (0.25-0.50)	0.23 (0.08-0.38)	0.54 (0.33-0.76)
Ultrafiltration (L)	3.48 (2.60-4.36)	2.69 (2.07-3.32)	2.54 (2.30-2.77)	2.27 (1.96-2.58)	2.34 (1.93-2.74)	2.35 (1.86-2.84)
Kt/V (per HD session)	1.05 (0.86-1.26)	1.06 (0.39-1.51)	1.05 (0.55-1.55)	0.98 (0.42-1.46)	1.1 (0.79-1.46)	1.08 (0.75-1.53)
Sodium intake (g/day)*	2.38 (1.29-3.45)	3.89 (2.41-5.37)	2.86 (2.22-3.16)	2.50 (2.20-3.14)	3.10 (2.09-4.34)	3.34 (2.54-4.55)

II) was used [15]. Patients were instructed on how to complete the questionnaire, and written instructions were provided. The analysis of the survey was performed by the computer program Diet Calc and adopted as the standard value by the most complex recommendations on HD patients' nutrition - K/DOQI Clinical Practice Guidelines for nutrition in chronic renal failure [16]. Nutritional status was assessed on the basis of anthropometric measurements (body mass and height) used to calculate body mass index (BMI; kg/m²), stratified in line with WHO recommendations for Caucasians.

Evaluation of hypertension and antihypertensive drug doses

Hypertension was diagnosed according to the 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension [17]: if average BP values from two measurements before HD session were equal to or higher than 140 mmHg (systolic BP) and/or 90 mmHg (diastolic BP), or if the patient was taking antihypertensive drugs over the past two weeks due to an earlier diagnosis of hypertension.

Hypertensive patients were assigned into five subgroups according to the number of antihypertensive drugs used in maximal recommended doses (adjusted to the status of kidney function). When the drug was used in a small dose (much less than half of maximal recommended dose in HD patient) – it was scored as ¼ of the drug; moderate doses were scored as ½ of the drug.

Statistical analysis

For the statistical analyze the 12.5 version of Statistica software (StatSoft, Cracow, Poland) was used. Data was presented as mean values ± standard deviation. Distribution of the examined variables was checked by Shapiro-Wilk test. Categorical variables were compared using χ^2 tests. To analyse the relationship between variables with normal distribution, Pearson correlation was used. In the case of nonparametric distribution of variables, correlations were calculated according to Spearman.

The receiver operating characteristic (ROC) was used for the establishment of cut-off values for the levels of NT-proBNP, CT-proAVP resulting in the use of at least 3 antihypertensive drugs in maximal doses.

The threshold for statistical significance was set at $\alpha = 0.05$.

Results

Patients characteristics

In the analyzed study group of HD patients, 145 (96.7%) were hypertensive. Among them, 131 were receiving antihypertensive medication (most frequently β -adrenolytics, calcium channel blockers and angiotensin converting enzyme inhibitors), including 19 on 3 or more drugs (calculated for maximal doses). Despite antihypertensive therapy, 31.0% of HD patients had mean blood pressure greater than 140 mmHg for systolic blood pressure (SBP) or 90 mmHg for diastolic blood pressure (DBP). Detailed patient characteristics, including anthropometric data, causes of CKD, concomitant diseases, dialysis parameters, pharmacotherapy of hypertension, and calcium-phosphate disorders was shown in Table 1 and 2.

Fig. 2. Receiver operator curve analysis showing the threshold for NT-pro BNP value (over 13,184 pg/mL) as a predictor of the use of at least 3 antihypertensive drugs in maximal doses in the therapy of hypertension.

Data concerning daily water and sodium intake on the basis of diet history questionnaire were obtained from 107 patients (71.3%). Mean daily sodium intake was estimated at 2.86 g.

NT-proBNP and CT-proAVP concentrations

Median plasma concentration of NT-proBNP was 6, 424 (2, 425 – 29, 306) pg/mL, and it was associated with systolic ($R=0.19$; $p=0.02$) but not diastolic BP values ($R=0.05$; $p=0.55$), and the number of received antihypertensive drugs ($R=0.21$; $p=0.01$). The highest NT-proBNP values were observed in patients receiving 3 or more antihypertensive drugs (Table 3).

Median plasma concentration of CT-proAVP was 2797 (2073 – 4289) pg/mL, and not correlated with BP values ($R=-0.03$; $p=0.68$ for SBP and $R=-0.01$; $p=0.92$ for DBP) as well as the number of antihypertensive drugs ($R=-0.04$; $p=0.64$).

Furthermore, there was no correlation between concentrations of NT-proBNP and CT-proAVP. Looking for NT-pro BNP and CT-proAVP values characteristic for patients necessitating antihypertensive polytherapy with at least 3 antihypertensive drugs we used receiver operator curve analysis. This analysis showed that NT-pro BNP values over 13, 184 pg/mL predicted the use of at least 3 antihypertensive drugs in maximal doses in the therapy of hypertension (Figure 2), similar analyses performed for CT-proAVP showed much less specificity (Figure 3).

Fig. 3. Receiver operator curve analysis showing the threshold for CT-pro AVP (below 3,185 pg/mL) as a predictor of the use of at least 3 antihypertensive drugs in maximal doses in the therapy of hypertension.

Discussion

The assessment of overhydration in haemodialysis patients with evident clinical symptoms (presence of pedal edema, basilar rales, enlargement of carotid veins and other) and severe hypertension is usually quite easy. However, in the case of HD patients without clinical symptoms of overhydration but requiring multidrug hypertension therapy, biochemical markers like NT-proBNP or CT-proAVP seem to be useful for identification of volume overload.

Our results demonstrated that high values of NT-proBNP (over 13,184 pg/mL) were characteristic for HD patients requiring multidrug antihypertensive therapy, which could not be demonstrated for CT-proAVP. Therefore, we assume that NT-proBNP is a better marker of hypervolemia assessment in HD patients, as hypervolemia is a frequent cause of resistant hypertension. Previously NT-proBNP levels higher than 5, 300 pg/mL were shown as associated with volume overload in HD patients and highly predictive of cardiovascular mortality [18]. In line with this study, our data suggest that assessment of NT-proBNP have potential to identify HD patients with resistant hypertension, probably due to volume

overload and in consequence increased the risk of cardiovascular morbidity and mortality. Moreover, our data suggests the need for reinforcing ultrafiltration and reduction of post-dialysis body mass in hypertensive patients with higher NT-proBNP levels.

It should be emphasized that, although NT-proBNP can reflect changes in hydration status [19], it is also influenced by preload volume and left ventricular heart failure as well as left ventricle hypertrophy (LVHT) [20, 21]. In patients without residual renal function, both an accumulation and the impairment of its biodegradability may frequently occur [22]. However, the volume overload may characterize patients with significant residual diuresis, but already impaired regulation of blood volume. Our study lacks the information about the exact percentage of HD patients with heart failure and LVHT, which should be considered as a major limitation.

The results of our study suggest that CT-proAVP concentrations seem to be a weaker marker of volume overload in HD patients. However, we have previously shown that its elevated concentration predicted a rapid weight loss after kidney transplantation and characterize the subgroup of patients with greater overhydration [23]. According to previous studies, regulation of CT-proAVP metabolism in patients with chronic kidney disease is disturbed [24, 25]. Plasma concentrations of CT-proAVP are greatly increased in haemodialysis patients, most likely reflecting its accumulation [26]. One of the possible explanations could be high osmolality of the extracellular fluid in ESRD patients, which is more dependent from an accumulation of uremic toxins, especially urea, but not sodium. New data assesses the role of CT-proAVP as a predictive marker of volume overload in HD patients. Kim et al. showed that CT-proAVP was in a positive correlation with pre-dialysis body fluid volume [27]. In another study CT-proAVP in HD patients was correlated with ultrafiltration volume, suggesting that volume depletion during dialysis might be responsible for its increase [28].

The main limitation of our study was the lack of blood volume assessment and performance of echocardiography. Therefore, we can only speculate that high blood volume was the cause for application of multidrug antihypertensive therapy. Lack of the other measures of fluid overload such bioimpedance measurement or inferior vena cava diameter should also be considered as an additional limitation of the study. Furthermore, the diagnosis of hypertension was based on BP measurements performed before haemodialysis sessions and no 24-hour ambulatory blood pressure measurement. However, such a method of BP control and antihypertensive therapy tailoring is most commonly used in daily clinical practice. It should be stressed that our study population was characterized by a very high prevalence of hypertension (96.7%), even greater than in German data from DOPPS register (95.6%) [29]. It is the result of the exclusion of patients with apparent volume overload that is a typical clinical manifestation of severe heart failure.

Conclusion

Increased levels of N-terminal prohormone of brain natriuretic peptide seems to be better than C-terminal pre-pro vasopressin (copeptin) biomarker of multidrug antihypertensive therapy requirement. Whether an estimation of N-terminal prohormone of BNP in these patients will be also better biomarker than copeptin in the prediction of CV complications related to hypertension needs further investigations.

Disclosure statement

All authors declare that there is no Disclosure Statement related to this paper.

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