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Original Paper

Vasoactive Peptide Levels after Change of Dialysis Mode

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Key Words

Vasoactive peptides · N-terminal fragment of pro-brain natriuretic peptide · Neuropeptide Y · Convective therapies · Hemodiafiltration

Abstract

Background/Aims: Plasma concentrations of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) are increased in end-stage renal disease. Improvement in hemodynamic stability has been reported when switching from hemodialysis (HD) to on-line hemodiafiltration (ol-HDF). The aim of this study was to investigate plasma concentrations of NT-proBNP, BNP and neuropeptide Y (NPY) during a 1-year follow-up, after a change from high-flux HD to postdilution ol-HDF. Additional variables were also studied, e.g. pulse wave velocity and ordinary clinical parameters. **Method:** We conducted a prospective, single-center study including 35 patients who were switched from HD to HDF. Plasma concentrations of NT-proBNP, BNP and NPY before and after dialysis were measured at baseline (i.e. HD) and at 1, 2, 4, 6 and 12 months on HDF. **Results:** All three peptide levels decreased significantly during HD and HDF when comparing concentrations before and after dialysis. Mean absolute value (before/after) and relative decrease (%) before versus after dialysis was 13.697/9.497 ng/l (31%) for NT-proBNP, 62/40 ng/ml (35%) for BNP and 664/364 pg/l (45%) for NPY. No significant differences were observed when comparing predialysis values over time. However, post-dialysis NT-proBNP concentration showed a significant decrease of 48% over time after the switch to HDF. **Conclusion:** The postdialysis plasma levels of NT-proBNP, BNP and NPY de-

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creased significantly during both dialysis modes when compared to before dialysis. The post-dialysis lowering of NT-proBNP increased further over time after the switch to ol-HDF; the predialysis levels were unchanged, suggesting no effect on its production in the ventricles of the heart.

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Introduction

Brain natriuretic peptide, or B-type natriuretic peptide (BNP), participates in the regulation of cardiovascular function. It is mainly produced in the ventricular myocytes, and the proBNP is cleaved into BNP₃₂ and N-terminal fragment (NT)-proBNP_{1–76}, which are both released into the blood stream with a half-life of 20 and 120 min, respectively [1]. BNP is active as a vasodilator and contributes to the relaxation of the myocardium. Plasma levels of BNP rise with decreasing left ventricular function and are used as biomarkers of heart failure. NT-proBNP likewise increases and has partly replaced BNP as a rapid diagnostic due to its stability and convenient determination. NT-proBNP is an important marker of left ventricular dysfunction, and the concentrations correlate with the left ventricular mass index and left auricular diameter [2]. NT-proBNP is therefore a potential marker for left ventricular remodeling, a common finding in patients with end-stage renal disease (ESRD). NT-proBNP seems to have an even greater prognostic value in patients with ESRD compared to other established cardiac biomarkers, e.g. troponin T (TnT) [3], even in asymptomatic hemodialysis (HD) patients [4]. NT-proBNP concentration is altered in ESRD patients, and increasing values are a risk factor for cardiovascular events and mortality in HD patients with type 2 diabetes mellitus [5] and HD patients in general [6]. In a recent study, an association of changes in NT-proBNP longitudinally with changes in inflammation, nutritional status, age and comorbidity was observed [7]. NT-proBNP has also been reported to be a predictor of early mortality (<1 year) in the dialysis population, even if the high-sensitivity TnT seems to be a better predictor for later mortality [8]. A significant decrease in BNP levels has been reported when changing HD frequency from 3 times per week to daily [9], and also NT-proBNP in some patients [10]. No difference was seen when comparing HD patients with peritoneal dialysis patients [11].

Neuropeptide Y (NPY) is a 36-amino acid polypeptide neurotransmitter found in the sympathetic nervous system and in the central nervous system. NPY exerts a role in various physiological functions, including the regulation of blood pressure, circadian rhythm, feeding behavior, anxiety, memory processing and cognition [12–14]. Plasma NPY is co-released with noradrenaline in response to sympathetic nervous stimulation and modulates the action of noradrenaline. NPY is also present in the heart and contributes to cardiovascular remodeling [15].

There has been a re-awakened interest in convective dialysis modalities since a new technology in dialysis machines and water purification has been implemented in dialysis units, especially in postdilution on-line hemodiafiltration (ol-HDF). Recently, a large randomized controlled study showed a lower risk of all-cause mortality, cardiovascular mortality and infection-related mortality in patients assigned to postdilution ol-HDF compared with patients on high-flux HD [16].

Frequent dialysis treatments improve markers of heart failure in the dialysis population [9, 17], but could a similar improvement be detected by increasing the efficiency of uremic toxins/middle-molecule removal by switching over to a convectional dialysis method such as ol-HDF? The aim of this study was to evaluate a 1-year follow-up in patients changing from HD to ol-HDF with respect to the levels of vasoactive peptides NT-proBNP, BNP and NPY.

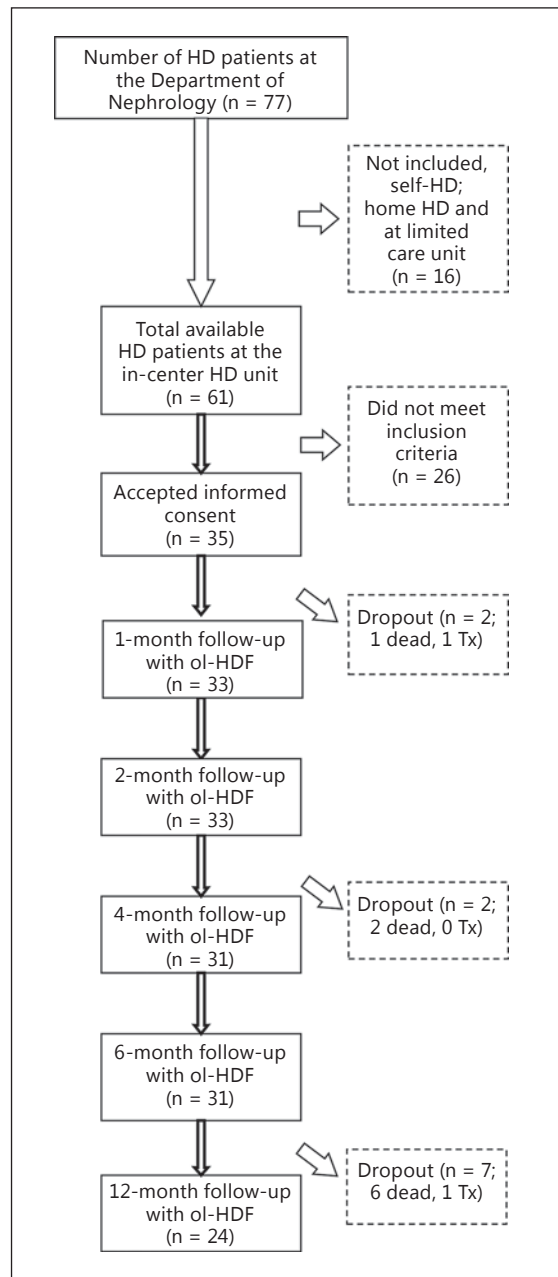


Fig. 1. Overview of the inclusion and dropout of patients during the study period. Tx = Transplantation.

Materials and Methods

Study Subjects and Design

Thirty-five patients on chronic HD from the Department of Nephrology, University Hospital, Linköping, Sweden, were included in the study. Figure 1 shows the patient flow through the study. The exclusion criteria were: patients that did not accept informed consent, did not understand the Swedish language, had a dysfunctional blood access and patients that were clearly in a palliative condition, i.e. dialysis time had been reduced and death was supposed to occur within a few weeks. This means that patients with serious heart failure were also included, as were patients with several other comorbidities (such as diabetes and

Table 1. Baseline characteristics of the 35 patients

	Mean ± SD	n
Duration of dialysis, months	46.9±53.9	35
BMI	25.5±4.2	35
Predialysis systolic blood pressure, mm Hg	147.4±29.0	35
Predialysis diastolic blood pressure, mm Hg	64.6±12.4	35
Dialysis time/week, h	11.6±2.5	35
Males/females		30/5
Age, years	70.8±12.5	35
Comorbidity (other diagnoses)		27
Malignancy		10
Pulmonary disease		4
Endocrine disease		1
Metabolic disease		1
Gastrointestinal disease		3
Neurological disease		2
Rheumatoid arthritis		2
Diabetes mellitus (type 1, n = 5/type 2, n = 7)		12
History of cardiovascular disease		24
Medication		
Vitamin D (alfacalcidol and/or paricalcitol)		32
Phosphate binders (lantan or sevelamer)		18
Calcium (calcium carbonate)		29
Calcimimetics (cinacalcet)		5
Antihypertensives (felodipin, enalapril, metoprolol, amlodipin, losartan, doxazocin, isosorbide mononitrate, irbesartan)		31

malignancy). The dialysis monitor used in all treatments was Fresenius 5008 (Fresenius Medical Care, Germany); the dialyzers used during HD (baseline) were FX 80, and during the ol-HDF period (12 months) FX 800 (Fresenius Medical Care), both with an effective membrane area of 1.8 m² and an ultrafiltration (UF) coefficient of 59 and 63 ml/h mm Hg, respectively. Both dialyzers had the same permeability for the middle molecule representative β_2 -microglobulin, a sieving coefficient of 0.8. The duration of the treatments varied between 180 and 270 min, the dialysate flow was 500 ml/min and the blood flow varied between 280 and 350 ml/min. The AutoSub system mode for calculation of the on-line prepared convection fluid volume (Vc) by the dialysis machine was used during all ol-HDF treatments, enabling automatic calculations based on parameters such as patients' total protein and hematocrit values. The Vc during the ol-HDF sessions varied between 10.1 and 28.3 liters per session (mean 20.3 ± 4.2 liters). Table 1 shows the characteristics of the included patients at baseline. A few sub-analyses (in the case of NT-proBNP) were also performed dividing data into a subset of patients: with or without a history of cardiovascular disease (CVD) and having diabetes or not.

Sampling Procedure

All samples from a total of 196 observed dialysis treatments were collected at the midweek session. Predialysis blood samples were collected after a 10-min rest in the lying position and postdialysis samples immediately after end of the same session still in the lying position. Immediately after the samples were collected, the test tubes were turned upside down 8–10 times and immediately placed on a wet ice bath. Within 60 min, the samples were centrifuged for 10 min at 2,000 rpm, and plasma was separated into 1.25-ml Cryotubes and placed in a freezer at a temperature below –70°C.

To validate, baseline samples were collected twice at the baseline period (i.e. the patient was treated with HD) at an interval of 1–2 weeks (B1 and B2). During the follow-up study period, samples were collected at 1, 2, 4, 6 and 12 months from the start of ol-HDF.

Measurements of the concentrations of NT-proBNP in plasma were performed using Cobas e 602 from Roche Diagnostics, and reagents from Roche (<http://www.cobas.com>). The total imprecision (% coefficient of variation) during 5 months of use was 3.8% at mean concentrations of 196 ng/l and 4.8% at 2,140 ng/l. Several patients had concentrations above the upper limit of the instrumentation, 35,000 ng/l. In those cases, a reanalysis was performed using a diluting buffer provided by Roche Diagnostics. Plasma samples were extracted using Sep-Pak® Plus C₁₈ reverse-phase cartridges (Waters, Milford, Mass., USA) before measuring the concentrations of BNP-32 and NPY. BNP-32 was measured using BNP-32 Human Fluorescent EIA kit (Nordic BioSite AB, Täby, Sweden). The lowest detectable concentration was 15.8 pg/ml, intra-assay coefficient of variation <10% and inter-assay coefficient of variation <15%. The concentrations of human NPY were measured using an in-house radioimmunoassay based on a rabbit antiserum NPY2151 (IC₅₀ = 24 pmol/l) raised against BSA-conjugated human NPY. ¹²⁵I-labeled and reverse-phase HPLC purified human NPY was used as radioligand and human NPY as calibrator. The lowest detectable concentration was 4 pmol/l. Intra- and interassay coefficients of variation were 6 and 11%, respectively. Samples were lacking from 3 patients; 1 got transplanted during the baseline period and 2 were found to be hepatitis C positive (not accepted at the laboratory).

Pulse Wave Velocity

Blood vessel elasticity was estimated using a tonometer (SphygmoCor®; AtCor Medical, Australia) to obtain a measure of the patients' general (aortic) vascular status. The measurements were performed, with connected ECG, by recording the pulse of the femoral and carotid artery on the opposite side.

Statistical Analyses

In some patients, the concentration values of NT-proBNP were extremely high (lowest 149.0 and highest 219,897.0 ng/l), yielding highly skewed data. Also highly skewed data were observed in BNP (lowest 0.004 and highest 1,306.9 ng/ml) and in NPY (lowest 2.0 and highest 2,932.9 pmol/l). Data were therefore logarithmically transformed (log₁₀) before analysis. No data were excluded. To validate the baseline, a comparison between values at baseline 1 (B1) and at baseline 2 (B2) using Student's t test was performed, showing no significant difference, $p > 0.05$. In cases where a comparison was made between two groups, Student's t test was used at the same p level as above. To investigate if there was a difference in mean concentration of peptides in plasma over the study period, ANOVA (repeated measure) was used and a p value <0.05 was considered as significant. Correlations between UF volume, systolic and diastolic blood pressure, pulse wave velocity (PWV), routine laboratory parameters, and the vasoactive peptides were also performed (Pearson correlation coefficient). The Regional Ethical Review Board approved (Dnr M153–07) the study protocol, and written informed consent was obtained from all patients.

Results

Figure 1 shows the number of included prevalent patients and dropouts during the study period. Of the total number of 61 available patients at our in-hospital dialysis unit, 26 did not meet the inclusion criteria, i.e. did not understand Swedish ($n = 11$), did not accept informed

Table 2. Additional patient data during the study period

	Baseline		6 months		12 months		p
	mean ± SD	n	mean ± SD	n	mean ± SD	n	
Hemoglobin, g/l	125.8±13.4	35	124.5±15.0	31	120.0±15.0*	24	0.04
Parathyroid hormone, ng/l	293.9±227.2	35	289.3±251.2	31	361.2±376.9	24	0.41
Ionized calcium, mmol/l	1.2±0.1	34	1.2±0.1	30	1.2±0.1	24	0.26
Phosphorus, mmol/l	1.8±0.7	35	1.6±0.4	31	1.5±0.5*	24	0.04
Albumin, g/l	35.0±4.6	35	35.4±5.4	31	35.6±4.3	24	0.88
CRP, mg/l	25.6±40.3	35	26.1±29.8	31	13.4±6.1	24	0.33
Predialysis systolic blood pressure, mm Hg	142.4±29.0	35	152.8±34.4	31	148.7±27.5	24	0.28
Predialysis diastolic blood pressure, mm Hg	64.6±12.4	35	68.8±17.6	31	68.9±15.5	24	0.64
Dialysis time/week, h	11.6±2.5	35	12.1±2.6	31	11.9±3.6	24	0.56
Predialysis urea, mmol/l	20.2±4.9	35	17.9±3.8*	31	16.9±4.3*	24	0.03
Kt/V, single pool	1.4±0.2	35	1.5±0.4	31	1.4±0.3	24	0.14
URR, %	68.8±6.4	35	71.8±7.9	31	71.4±7.4	24	0.08
Predialysis β ₂ -microglobulin, mg/l	24.9±7.3	33	22.3±7.3*	29	23.6±6.3	24	0.022
β ₂ -Microglobulin RR, %	56.4±8.0	31	73.4±8.8*	29	73.2±7.6*	24	<0.0001
PWV, m/s	12.2±6.0	26	11.7±5.0	13	12.3±4.6	15	0.92

URR = Urea reduction rate. * Significant vs. baseline (t test).

consent (n = 7), had too low access flow for ol-HDF (n = 4), were psychotic or had senile dementia (n = 3) or terminal condition (n = 1). The mortality rate was approximately 8.6% for the first 6 months and 25.7% for the whole year. All 9 patients who died during the study period had a history of serious cardiovascular incidents, and the cause of death was stroke (n = 2), acute myocardial infarction (n = 2), cardiac arrest (n = 2), ischemic leg resulting in amputation followed by infection (n = 2) and heart failure with septicemia (n = 1). As an example of early mortality, a few extreme values were observed, especially in the case of NT-proBNP, during the sampling period of 2 months, e.g. 1 patient had an analgesic pump with morphine for his severe angina pectoris and exhibited predialysis and postdialysis NT-proBNP values of 219.897 and 193.261 ng/l, respectively. This patient died a few days after that sampling. During the sampling period of 6 months, 1 patient had a pre- and postdialysis value of 171.067 and 173.233 ng/l, respectively; this patient suffered from a cerebral stroke a few days later and died after some days.

Table 2 presents additional data (routine laboratory data and PWV) of the patients from baseline (HD) and from 6 to 12 months of ol-HDF treatment. Statistically significant differences compared to baseline are highlighted in the table. The reduction ratio (RR) for β₂-microglobulin represents the most obvious change.

Figure 2 shows the patients' individual predialysis plasma values before and after the switch to ol-HDF for the 3 peptides, where HD is the mean of the two baseline predialysis values (B1, B2) and ol-HDF is the mean of the 5 follow-up predialysis values (1, 2, 4, 6 and 12 months) for each patient. No difference in predialysis values was found between HD and ol-HDF (p > 0.05).

Figure 3 presents the mean of the pre- and postdialysis values at group level; figure 3a for NT-proBNP, figure 3b for BNP and figure 3c for NPY. The postdialysis plasma values decreased significantly for all peptides when compared to predialysis (p < 0.05). Mean absolute values (before/after) and relative decrease before versus after dialysis was 13.697/9.497 ng/l (31%) for NT-proBNP, 62/40 ng/ml (35%) for BNP and 664/364 pg/l (45%) for NPY. The postdialysis NT-proBNP decreased significantly during the ol-HDF period (p < 0.0001), showing a mean value at baseline of 11.004 ng/l and 5.760 ng/l (48%) at 12

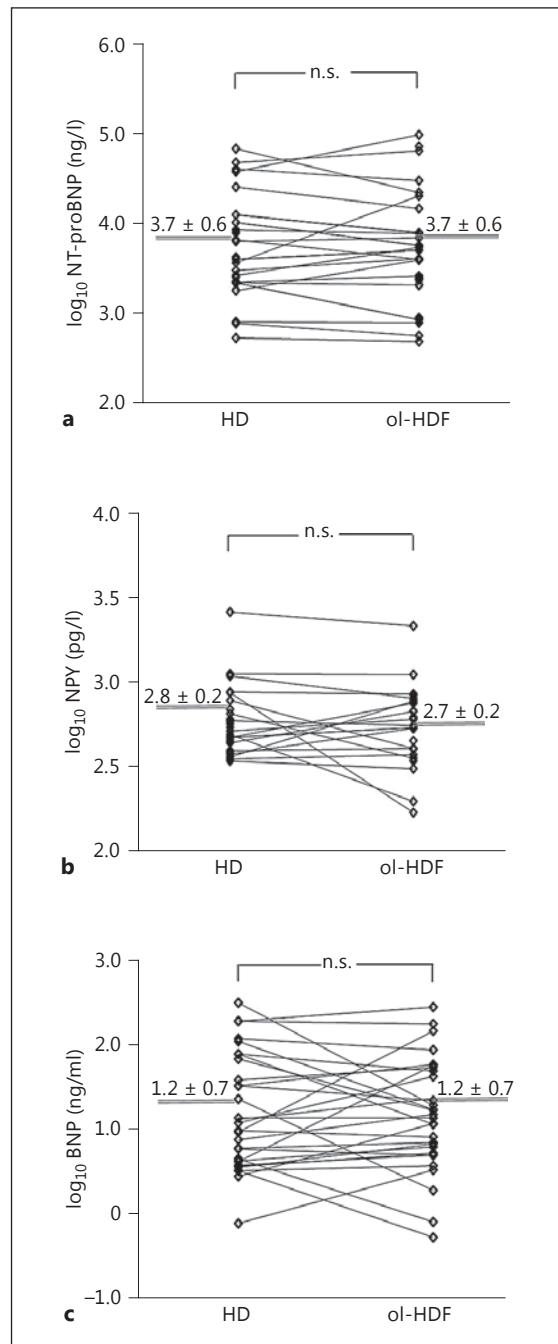


Fig. 2. The individual values (mean \pm SD) during HD (mean of the 2 baseline values, B1 and B2) and during ol-HDF (mean of the up to 5 follow-ups, depending on dropout).

months but remained unchanged for the other peptides ($p > 0.05$). In the case of predialysis values, no significant difference was observed over the 12-month period ($p > 0.05$).

Figure 4 shows the material when divided into subgroups of mean NT-proBNP; an overall lower NT-proBNP was seen in patients without a history of CVD (fig. 4a) and in patients without diabetes (fig. 4c) compared to the patients with a history of CVD (fig. 4b; $p = 0.001$) and diabetes (fig. 4d; $p = 0.01$). The picture is similar in the 4 subgroups as seen for the whole material, a greater reduction of postdialysis values during ol-HDF (1, 2, 4, 6 and 12 months) compared to HD (B1 and B2). It was noted that in the group of 9 patients without a history of

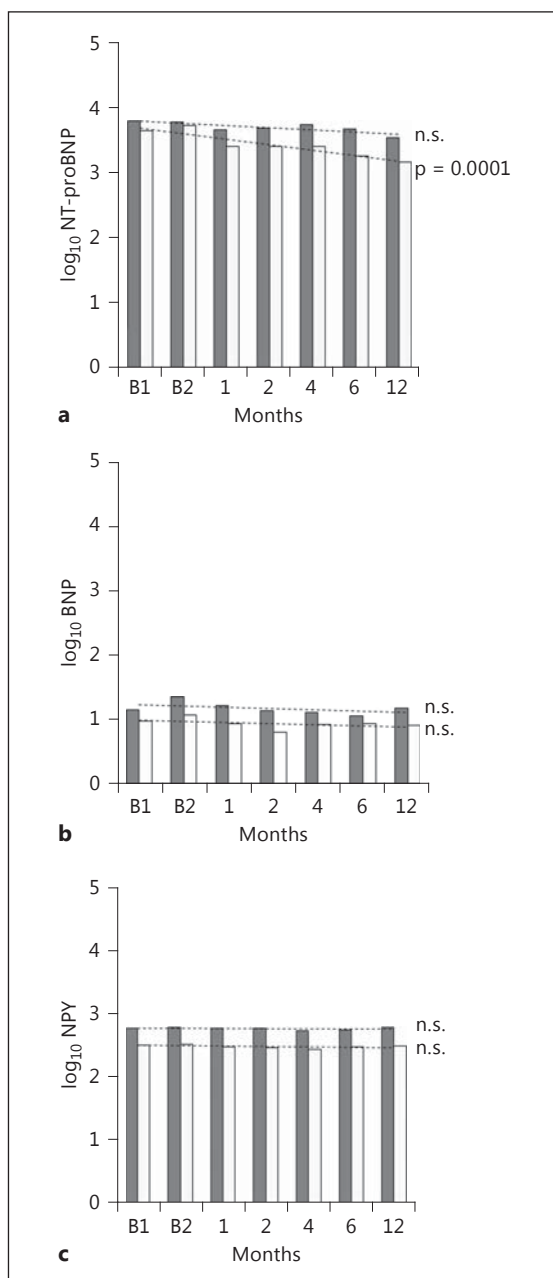


Fig. 3. Mean of pre- and postdialysis values, on group level, divided into sampling periods, where B1 and B2 are baseline, i.e. patients on HD, and the numbers 1–12 are months on HDF. The grey and white bars are pre- and postdialysis, respectively. A dashed trend line is also marked out for pre- and postdialysis values separately. Only the postdialysis NT-proBNP concentration was significantly decreased over time ($p = 0.0001$).

CVD (fig. 4a), none died during the 12 months of follow-up. This group also had much lower NT-proBNP values compared to the others; the mean of 63 predialysis NT-proBNP values was 4.549 ng/l compared to 18.120 ng/l for the CVD group (a mean of 133 predialysis values; $p = 0.001$).

Figure 5 presents scatterplots of predialysis concentration values of NT-proBNP versus BNP and NT-proBNP versus NPY in all studied sessions ($n = 196$). A significant correlation ($p < 0.05$) between NT-proBNP and BNP was seen ($r = 0.59$). No correlation between peptide concentrations and the other included routine clinical parameters and PWV (listed in table 2) was found ($p > 0.05$).

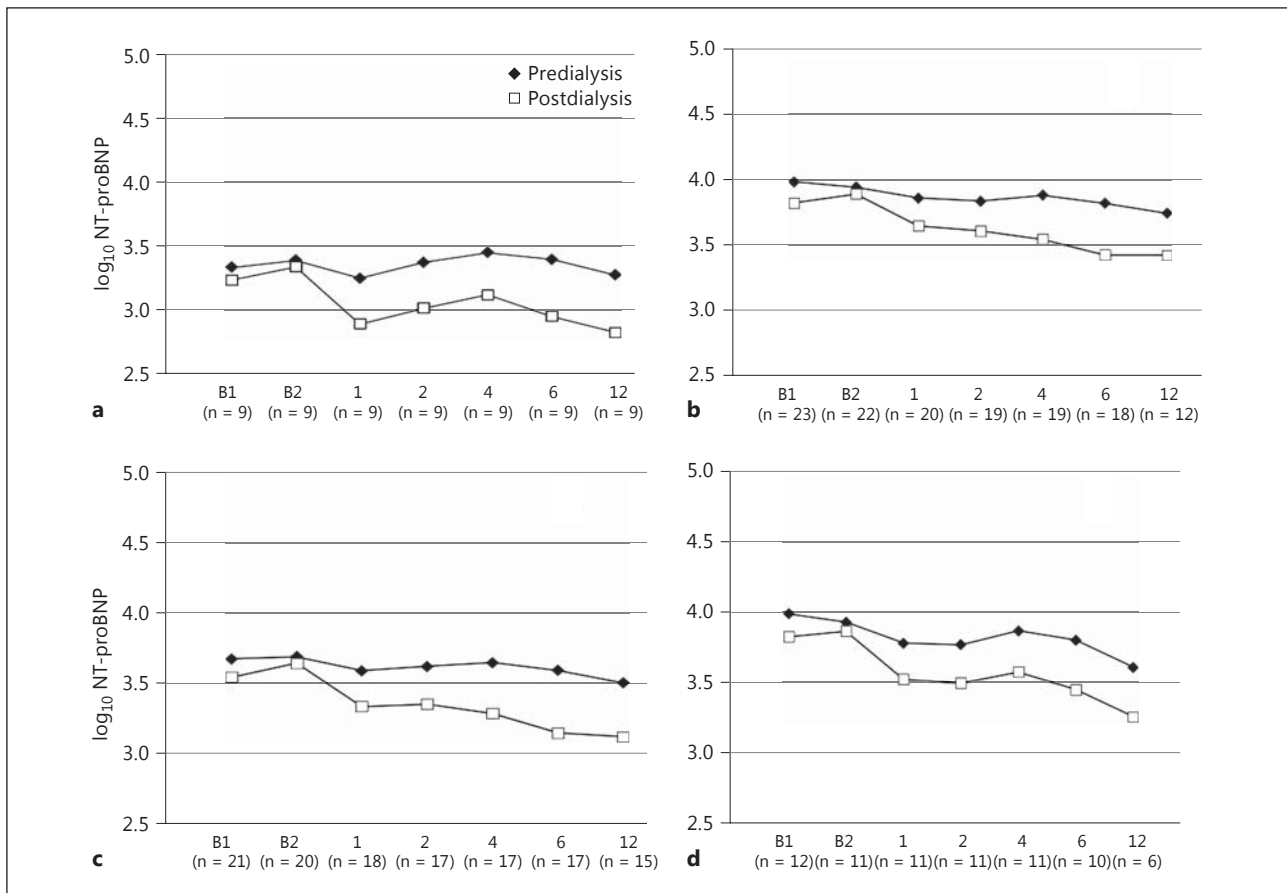


Fig. 4. NT-proBNP for the participating patients divided into subsets: no history of CVD (a), history of CVD (b), nondiabetics (c) and diabetics (d). The number of patients (n) at each time is also shown. A similar removal pattern is seen independently of the subset, but differences in overall concentration levels are notable. A slightly larger discrepancy can be seen between pre- and postdialysis values when patients were transferred to HDF.

Discussion

Plasma concentration (before vs. after dialysis) of the vasoactive peptides NT-proBNP, BNP and NPY decreased significantly during both high-flux HD and ol-HDF possibly due to unloading of the heart and elimination of the peptides during dialysis. The predialysis concentrations did not change significantly over time after switching over from HD to ol-HDF (fig. 2, 3), but the postdialysis NT-proBNP decreased significantly for ol-HDF and additionally showed a trend to decrease more over time (fig. 3a), which may be a result of a larger elimination compared to HD and/or due to the fact that patients with severe heart disease died early in the study. The molecular size of NT-proBNP is 8.5 kDa [18] (BNP 3.5 and NPY 4.3 kDa), which is lower than the cutoff for the dialyzers that were used, e.g. both dialyzers in the present study (FX80 and FX800) have a sieving coefficient of 0.8 for β_2 -microglobulin (molecule size 12 kDa). Earlier, Wahl et al. [18] have shown that natriuretic peptides such as NT-proBNP are eliminated during HD since this peptide has also been quantified in spent dialysate. A recently published study by Laveborn et al. [19] also demonstrates a significant decrease (before vs. after dialysis) in NT-proBNP and TnT with high-flux membranes, but

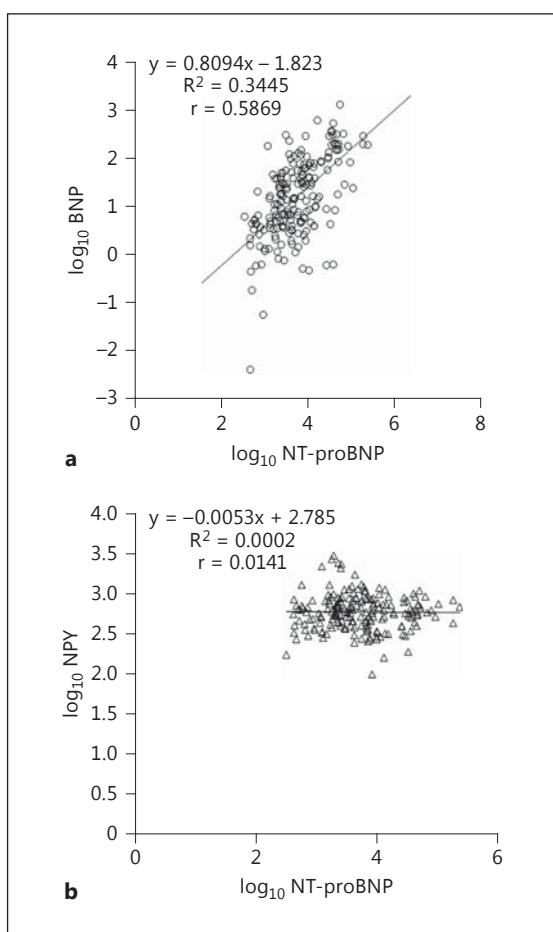


Fig. 5. Scatterplots of NT-proBNP versus BNP (**a**) and NT-proBNP versus NPY (**b**).

slightly the opposite levels with low-flux membranes. Due to the nonsignificant reduction of the predialysis plasma peptides and the equal sieving coefficients of the dialyzers used, it could be assumed that the convective effect is the main cause of the results in this study and not a considerable improvement in cardiac function. Plasma BNP and NT-proBNP reflect hemodynamic myocardial stress independent of the underlying pathology [1]. Most dialysis patients have an increased ventricular wall stress due to fluid volume and pressure overload on the heart, and their severity and prognosis can be estimated with NT-proBNP and BNP concentrations. Plasma NPY concentrations may increase with fluid and pressure overload, but this seems unlikely in the present study since there was no correlation between NT-proBNP and NPY concentrations (fig. 5b). The stress of the cardiovascular system was not markedly reduced with convective therapy, as reflected by predialysis vasoactive peptide concentrations in this study. Other studies of more frequent treatment have demonstrated a repeal of dialysis-induced myocardial stunning which was attributed to frequent HD due to alteration of UF volume and UF rate [9, 17]. The UF volumes during the observed 196 dialysis sessions in the present study were, in mean \pm SD, 1.75 ± 0.88 liters, which is a reasonably 'normal' UF volume (approx. fluid overload), and no correlation was found between NT-proBNP and either UF volume or blood pressure. However, postdialysis NT-proBNP values have been found to correlate with volume status in HD patients, especially in those without a history of cardiac disease or hypertension, and may be a guide for determination of target weight for HD patients [20]. In contrast to our 12-month study, a

survival study by Sivalingam et al. [21] showed that patients on HDF had significantly lower levels of both BNP and NT-proBNP compared to patients receiving high-flux HD during a 4-year follow-up. In contrast, in a recent randomized study of cardiovascular parameters, no improvement of arterial stiffness in PWV (m/s) was seen in patients on ol-HDF [22], which is in line with our PWV results (table 2). Of the 9 patients who died during the study period, all but 1 had a history of CVD and higher NT-proBNP. This is consistent with previous studies where NT-proBNP has been reported to be a good predictor of early mortality (<1 year) in the dialysis population [8]. In another recent study, only NT-proBNP was found to be a strong predictor for overall mortality in asymptomatic HD patients and did not improve the prediction of all-cause mortality when combined with high-sensitivity cardiac TnT [23]. As expected, the RR of β_2 -microglobulin increased significantly after the switch, but the predialysis values of β_2 -microglobulin were in the same order independent of dialysis mode (table 2). A Vc of >21.95 liters has been reported to be advantageous for reducing mortality [24], and in this study, the mean Vc was 20.3 liters but with a wide distribution from 10.1 to 28.3 liters. An increase in ol-HDF frequency and/or higher Vc are two possible ways to improve the uremic and fluid-overloaded milieu for this patient group. Perhaps an early or immediate start of ol-HDF will reduce some of the long-term negative effects for dialysis patients, thus resulting in better survival.

Future studies, preferably randomized, on a larger number of patients and during a longer follow-up period treated with high-volume ol-HDF are needed in order to clinically confirm beneficial effects with a lowering (and/or an increased elimination) of levels of vasoactive peptides in general, as shown by lower levels of cardiovasoactive peptides.

Limitations

The limitations to this study included small sample size, no comparator/randomization, no data concerning residual renal function and additional cardiac parameters.

Conclusion

Predialysis peptide concentrations, which most likely have a clinical importance, were not altered for any of the vasoactive peptides (NT-proBNP, BNP and NPY) when switching from high-flux HD to ol-HDF, suggesting no effect on its production in the ventricles of the heart. However, the concentration of NT-proBNP decreased significantly after dialysis following the switch to ol-HDF, assuming there was a larger elimination when compared to HD and/or that a significant number of patients with severe heart disease died early in the study.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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