INFLUENCE OF RESIDUAL DIURESIS ON CARDIAC BIOMARKER NTproBNP IN CHRONIC HEMODIALYSIS PATIENTS

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Abstract

High levels of cardiac biomarker N-terminal probrain type natriuretic peptide (NTproBNP) are present in hemodialyzed population and are associated with increased cardiovascular morbidity and mortality risks. Factors influencing the increase of NTproBNP and its significance in dialysis patients are still a matter of debate. We conducted a study on a cohort of 3 months-old chronic hemodialyzed patients in order to reveal the relationship between NTproBNP levels and residual diuresis, volume status, intradialysis ultrafiltration (UF), left ventricular ejection fraction (LVEF). Weekly, for 3-months, we measured for each patient the following parameters: NTproBNP levels, volemic status, UF rate and LVEF, before and after the first hemodialysis session in the week. The comparison between the three groups was discussed and analyzed. There was a significant inverse correlation between NTproBNP values and diuresis in all three studied groups, both before and after the dialysis sessions.

Rezumat

Valori crescute ale NTproBNP au fost observate la populaţia hemodializată, acestea fiind asociate cu creşterea riscului morbidităţii şi mortalităţii cardiovasculare. Factorii responsabili de creşterea nivelului de NTproBNP şi, de asemenea, impactul asupra evoluţiei pacienţilor dializaţi reprezintă încă o problemă controversată şi insuficient elucidată. Scopul prezentului studiu, care a inclus pacienţii hemodializaţi cronic de cel puţin 3 luni de zile, este de a observa dacă există o corelaţie între valorile NTproBNP şi diureza reziduală, volemie, ultrafiltrare, fracţia de ejecţie a ventriculului stâng. Timp de 3 luni, pentru fiecare pacient, la începutul şi sfârşitul primei şedinţe de dializă din săptămână, s-au evaluat următorii parametri: nivelul de NTproBNP, statusul volemic, rata de ultrafiltrare şi fracţia de ejecţie. Datele au fost comparate şi analizate între cele 3 grupuri de bolnavi. O semnificativă relaţie de inversă proporţionalitate s-a evidenţiat între valorile NTproBNP (pre- şi postdializă) şi diureză în toate cele 3 grupuri.

Keywords: hemodialysis, diuresis, volemia, ultrafiltration, left ventricular ejection fraction

Introduction

In hemodialyzed (HD) patients, significant diuresis is associated with preserved residual renal function (RRF) [1-3] and it is accompanied by better prognosis and reduced general and cardiovascular mortality [1-8], even in the presence of a decreased dialysis dose [6, 9-12]. With respect to volemic complications, oliguria is associated with poor control of systemic hypertension, need for unpredictable ultrafiltration (UF) rate and high risk

of intradialysis hypotension and increased incidence of cardiac failure [4, 6, 12, 13].

In the same time, several researches highlight excessive increase of cardiac biomarker N-terminal probrain type natriuretic peptide (NTproBNP) in chronic HD population [14-16] and its association with increased cardiovascular morbidity [14-21]. Still, the literature data are conflicting regarding either the causes or the significance of this increase [22, 23]. Thus, in different studies, the elevated levels of NTproBNP in hemodialysis are associated with decreased renal clearance [14, 17, 24, 25], different removal by dialysis [25, 26], malnutrition [17, 19, 25], volume overload [17-19, 25] or intrinsic cardiac disease [17-21, 24, 25]. Presence of large variations between individuals and a less pronounced within-individual variations may lead to misinterpretation of the results and may alter the significance of NTproBNP increase [27].

Materials and Methods

Between January 2012 and December 2014, 98 end-stage renal disease (ESRD) patients, with at least 3 months-history of chronic HD in the Dialysis Center of "Sf. Ioan" Emergency Clinical Hospital, 3 times *per* week with polysulfone high-flux dialyzers, were included in the study. Informed consent was obtained in all patients and the study was approved by Local Ethical Committee according to the laws in force.

Inclusion criteria were, besides dialysis dependence, lack of cardiovascular symptoms, absence of severe malnutrition (serum albumin < 2.5 g/dL), Kt/V (K = dialyzer clearance of urea; t = dialysis time; V = volume of distribution of urea, approximately equal to patient's total body water) > 1.2 during the 3 months study. Presence of asymptomatic non evolutive myocardial ischemia on electro-cardiogram (ECG) or asymptomatic alterations of left ventricular ejection fraction (LVEF) on ultrasound exam were not exclusion criteria.

Depending on the residual diuresis (mL/day), the patients were divided in three groups: group A ≤ 500 mL/day, group B between 500 - 1200 mL/day, group C ≥ 1200 mL/day. For each patient, the following parameters were measured before and after the first dialysis session of every week, for 3 months consecutively (24 variables for each parameter/patient).

NTproBNP was measured from blood samples taken from the arterial line, before anticoagulant administration, at the beginning of dialysis and from the venous line at the end of the dialysis sessions. NTproBNP assay was performed using an automatic analyser *Mitsubishi Kagaku PATHFAST Iatron Inc.*, whose principle is based on CLEIA procedure (*Chemiluminescent Enzyme Immunoassay*).

The device uses whole blood or plasma samples and detects concentrations of NTproBNP between 15 - 30,000 pg/mL; the reagents kit is manufactured by Roche and 2 were required for the present study (each contained sufficient materials for 60 determinations).

In order to minimize the effect of postdialysis haemoconcentration on the changes of blood levels of NTproBNP, we also measured predialysis and postdialysis hemoglobin (Hb). Therefore, we considered the real value of postdialysis NTproBNP (postdialysis rNTproBNP):

postdialysis rNTproBNP = measured postdialysis NTproBNP x postdialysis Hb/predialysis Hb.

Postdialysis real variation of NTproBNP (rvNTproBNP) was:

rvNTproBNP = predialysis NTproBNP - rNTproBNP,

and to express the percentage of real postdialysis changes of NTproBNP, we calculated:

rvNTproBNP / predialysis NTproBNP x 100 = % NTproBNP.

In most cases it is expected that NTproBNP levels would decrease after each dialysis session at least for two reasons: removal of the cardiac marker in the high-flux dialyzers and decrease of plasma volume as a consequence of UF (therefore the extent of myocardial wall stretch which stimulates the secretion of NTproBNP is smaller). In this case, we noted the intradialysis percentage changes with +%; if NTproBNP increased after dialysis, the percentage change was noted with -%.

Predialysis and postdialysis volemia were measured by transthoracic vascular bioimpedance method, using the apparatus *Hotman, Tebco (Integrated Hemodynamic Management System)*. With this device, the results are displayed as percentages; we considered hypervolemia at levels higher than 120%, normovolemia between 80 - 120% and hypovolemia below 80%.

Intradialysis ultrafiltration was calculated as:

UF% = intradialysis UF/dry weight x 100.

LVEF (normal values ≥ 55%) was measured by 2D-echocardiography using the modified Simpson method, from apical 4 chamber view (the ventricle volume was appreciated by total sum of the stack of elliptical disks). A modification of more than 10% compared with anterior value was considered significant.

Statistical analysis

The comparison of the results between the three groups were discussed and analysed with following tests: T-test, χ^2 test and Pearson correlation

coefficient. Statistical analysis was performed using Excel and IBM SPSS Statistics v. 20.0.

Results and Discussion

The three groups consisted of: group A (diuresis ≤ 500 mL/day) – 38 patients (21 men, 17 women, mean age of 53.3 years); group B (diuresis between 500 - 1200 mL/day) – 36 patients (23 men, 13 women, mean age of 49.7 years); group C (diuresis ≥ 1200 mL/day) – 24 patients (11 men, 13 women, mean age of 63.2 years) (Figure 1).
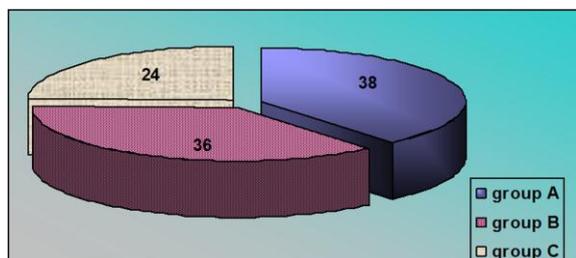
Figure 1.
Number of patients included in each group of the study

Results in group A:
Predialysis NTproBNP ranged between 5,723 - 13,872 pg/mL, with an average of 7,099 pg/mL. The adjusted postdialysis NTproBNP ranged between 3,987 - 10,087 pg/mL, with an average of 5,721 pg/mL. The percentage of NTproBNP changed after dialysis was between -17.94% and 43.04%, with an average of 19.41%.

Volemic status at the beginning of dialysis session revealed hypervolemia in 86.84 - 92.10% of the patients (mean 90.13%), euvolemia in 5.26 - 13.15% of cases (mean 9.21%) and hypovolemia from 0 to 2.63% of the individuals (mean 0.66%). After dialysis, hypervolemia was present in 10.52 - 15.79% of the subjects (mean 12.06%), normovolemia in 26.31 - 31.58% (mean 28.95%) and hypovolemia in 52.63 - 63.15% (mean 58.99%).

Between dialysis, the weight increase in group A varied between 6.7 to 1.8 kg (mean 4.2 kg), representing 2.43 - 8.40% of the patients' dry weight (mean of 5.25% from dry weight). Dialysis UF ranged between 2.57 and 7.54% of the dry weight (mean 5.08%).

Results in group B:
Predialysis NTproBNP varied between 2,604 - 9,876 pg/mL (average 3,221 pg/mL). The adjusted postdialysis NTproBNP ranged between 1,065 - 3,121 pg/mL (average 1,936 pg/mL). The percentage of NTproBNP change after dialysis was between 12.02% and 68.39% (average 39.89%).

Before dialysis, transthoracic bioimpedance revealed in group B hypervolemia in 75 - 83.33% of patients (mean 79.16%), normovolemia in 13.88 - 16.66%

(mean 15.97%) and hypovolemia in 2.77 - 8.33% (mean 4.86%). After dialysis, incidence of hypervolemia varied between 13.88 - 16.66% of subjects (mean 14.81%), normovolemia between 77.77 - 83.33% (mean of 80.32%) and hypovolemia between 2.77 - 5.55% (mean 4.86%).

Between dialysis, the weight increase in group A varied between 0.8 - 4.1 kg (average 2.6 kg), representing 1.6 - 5.2% of the patients' dry weight (mean of 2.96% from dry weight). Dialysis ultrafiltration ranged between 1.6 - 4.87% of the dry weight (mean of 2.81%).

Results in group C:
Before dialysis, NTproBNP varied between 489 - 4,302 pg/mL (average 1,301.37 pg/mL). The adjusted postdialysis NTproBNP ranged between 247 - 1,121 pg/mL (average 607.75 pg/mL). The percentage of NTproBNP change after dialysis was between 27.55% and 71.85% (average 53.30%).

Measurement of volemia revealed in group C, before dialysis, hypervolemia in 20.83 - 50% of patients (mean 34.02%), normovolemia in 41.66 - 62.50% (mean 54.16%) and hypovolemia in 8.33 - 16.66% (mean 11.80%). After dialysis, the distribution of volume status in group C revealed hypervolemia in 4.16 - 8.33% of the individuals (mean of 6.25%), normovolemia in 87.50%, and hypovolemia in 4.16 - 8.33% (mean 6.25%).

Between dialysis, the weight increase in group C, ranged between -0.3 kg and 1.8 kg (mean 0.72 kg), representing a percentage of -0.53% and 2.2% from the dry weight (mean of 0.9% from dry weight). In this group, dialysis UF was identical with the expected weight elevation in patients presenting weight deficit and minimal programmed UF; therefore, UF varied between 0 and 2.2% of the patient's dry weight (mean of 0.9%).

Echocardiography in the three groups
In group A, mean LVEF at the beginning of the study was 57.24% (with limits between 43% and 58%), in group B 58.5% (with limits between 42% and 65%) and in group C the mean LVEF was 57.9% (with limits between 48% and 64%) (Figure 2).
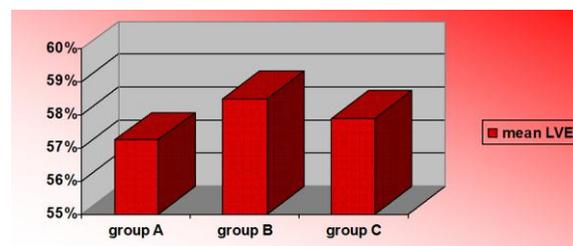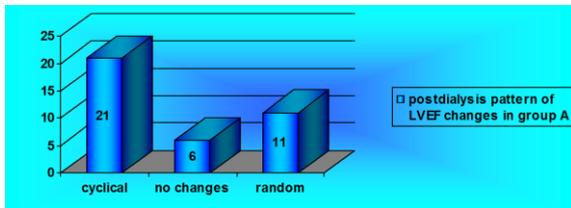

Figure 2.
The mean left ventricular ejection fraction in the three groups at the beginning of the study

During the dialysis sessions, in group A, we noticed three patterns of LVEF changes (Fig. 3). Significant decrease of LVEF in all dialysis sessions, with

more than 10% of the predialysis value (12 to 18%) was noticed in a number of 21 patients. We observed that this decrease was not permanent since, at the next session, the ultrasound showed an LVEF value with minor changes (below 10%) compared with the previous predialysis LVEF measurement. We classified this pattern of LVEF changes as cyclical. Although some patients have decreased their LVEF values at the end of the 3 month study per patient when compared with baseline; these decreases were below the levels that we initially considered as being significant (less than 10% of initial LVEF) and, therefore, we considered them irrelevant. No significant changes of LVEF (meaning changes of > 10% from the value before the dialysis session) after any of HD sessions have been highlighted in a number of 6 patients. In the remaining patients (11 cases), we considered postdialysis changes of LVEF as random because we could not fit them into a pattern; in several dialysis sessions there was a cyclical pattern of LVEF decrease, than we noticed a stabilization of LVEF or minor changes; other patients had cardiovascular complications that permanently altered LVEF throughout the study (2 had intradialysis angina, one patient presented severe bronchopneumonia complicated by malnutrition, worsening an asymptomatic previous heart failure).
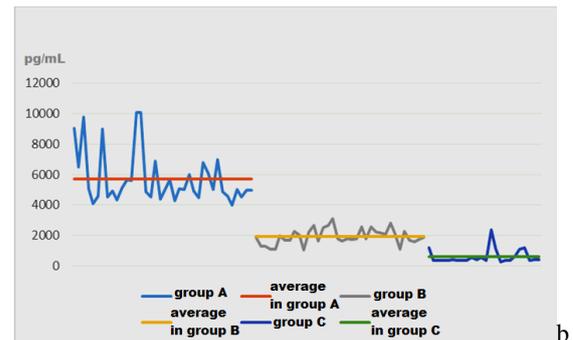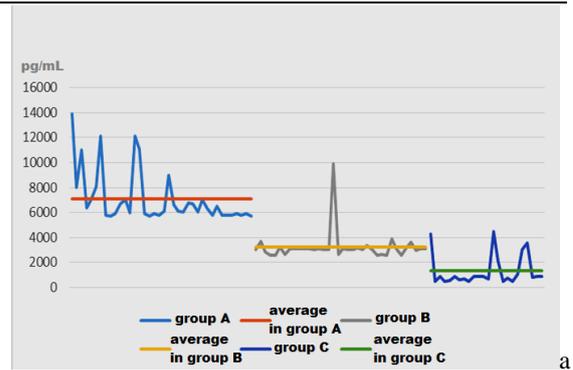

Figure 3.

Postdialysis pattern of LVEF changes in group A

When comparing the results obtained in the three groups of patients, we noticed that the average value of NTproBNP was significantly greater in group A when compared with the other two groups of patients, both before the dialysis sessions (t test, p < 0.0001) and after the dialysis sessions (t test, p < 0.0001) (Figure 4 and 5).
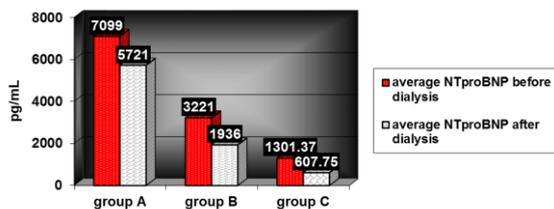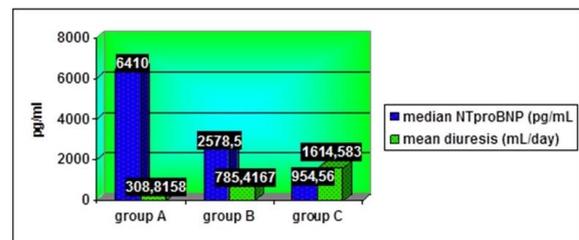

Figure 4.

The average values of NTproBNP in the 3 groups of patients before and after dialysis sessions

Figure 5.

Variations of NTproBNP median values (pg/mL) in the 3 groups of patients before (a) and after (b) dialysis sessions

It was observed a clear relationship between median value of NTproBNP (average predialysis NTproBNP + average adjusted postdialysis NTproBNP/2) and median residual diuresis (Figure 6). Measuring the percentage by which NTproBNP decreased during HD sessions, it was noticed that in group A it occurred the smallest decline of NTproBNP after dialysis when compared to the other two groups (t test, p between < 0.0001 and 0.0253) (Figure 7); therefore, in group A the mean NTproBNP decreased by only 19.41%, while in group B there was recorded a 39.89% decrease and in group C a decrease of 53.30% when compared with predialysis levels (postdialysis adjusted NTproBNP – predialysis NTproBNP / predialysis NTproBNP x 100) (Figure 8).

Figure 6.

Median values of residual diuresis and NTproBNP in the three studied groups

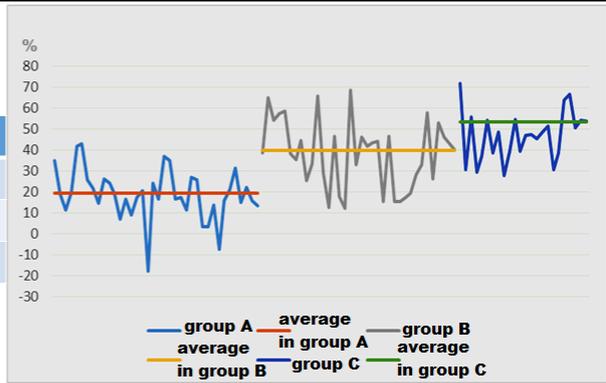| Groups of patients	S_d	T	p
Group A vs Group B	202	5.83	< 0.00001
Group B vs Group C	212	2.30	0.0253
Group A vs Group C	143	8.99	< 0.00001

Figure 7.
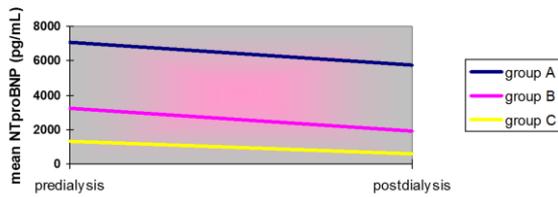The percentage by which NTproBNP has decreased during the dialysis sessions

Figure 8.
The decreasing rates of mean values of NTproBNP during the dialysis sessions in the three groups

When comparing the results regarding volemia, statistical analysis highlighted that before dialysis there was a significant higher incidence of hyper-volemia in group A, as expected (χ^2 test). In the same time, after dialysis sessions, again in group A, it was recorded a significantly higher incidence of hypovolemia when compared with the other two groups (χ^2 test) (Figure 9).
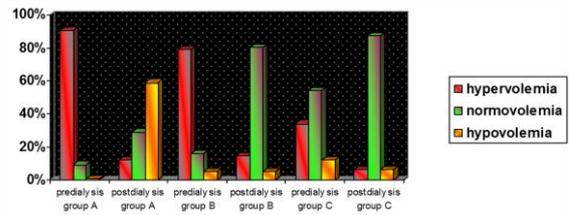

Figure 9.
The incidence of volemia disturbances before and after dialysis in the three groups

Statistical analysis also emphasized that, in group A, but not in the other two groups of patients, the presence of postdialysis hypovolemia was associated with the lowest decrease of NTproBNP during the dialysis sessions. Instead, both in group B and in group C, postdialysis hypovolemia was associated with significantly important decrease of NTproBNP (Figure 10).
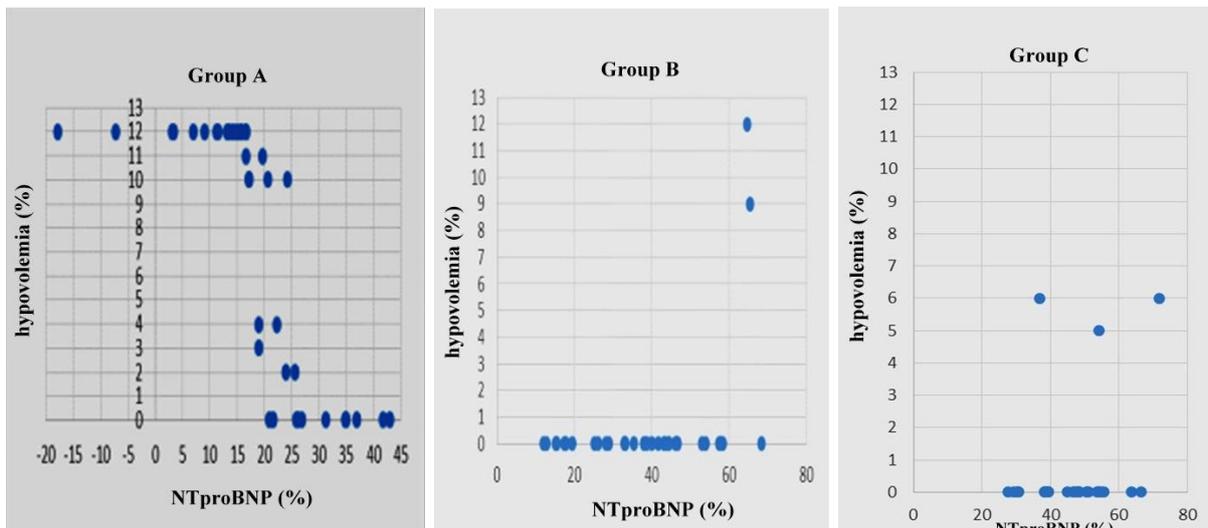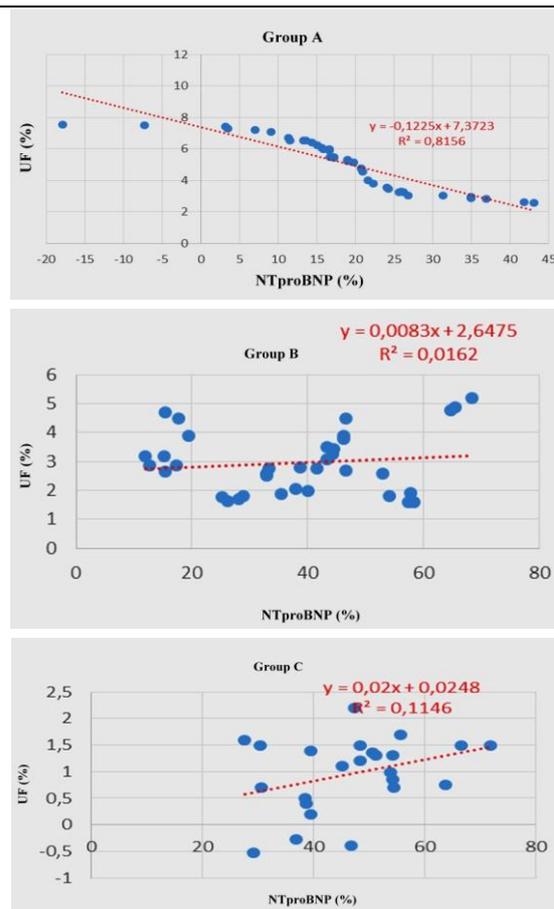

Figure 10.
The association between variations of volemia and NTproBNP values during the dialysis sessions in the three groups

Interestingly, in the same group, but not in the other two groups, a significantly inverse relationship was found between dialysis UF expressed as a percentage of dry weight and decrease of NTproBNP during dialysis (Pearson correlation coefficient, R2 = 0.8156 in group A, R2 = 0.0162 in

group B, and R2 = 0.1146 in group C, respectively) (Figure 11).

Regarding the alterations of LVEF during the dialysis sessions – significant only in group A – analysis of the results revealed that the three patterns of LVEF after dialysis correlated with the degree of NTproBNP reduction during the dialysis sessions (Tables I and II) (t test – p between 0.0980 and 0.8080) (Figure 12). All patients with cyclical variations of LVEF had the smallest reduction of NTproBNP after dialysis sessions, between -17.94% and 15.03%. Patients with no alterations of LVEF during dialysis sessions had the greatest reductions of NTproBNP, above 31.28% (limits between 43.04 - 31.28%). Patients with random, variation changes of LVEF after dialysis sessions had a reduction of NTproBNP between 26.83% and 15.64%.

Figure 11.
The relation between UF (100% of dry weight) and NTproBNP variations during the dialysis sessions in the three studied groups

Table I

Average diuresis and median NTproBNP before and after dialysis in patients with cyclical decrease of LVEF (group A)

Median diuresis (mL/day)	Predialysis median NTproBNP (pg/mL)	Postdialysis median NTproBNP (pg/mL)	Percentage of postdialysis changes of NTproBNP (%)
125	8031	6509	18.95
200	11004	9760	11.3
360	6340	5090	19.71
100	5730	4908	14.34
450	7012	5679	19.01
350	6009	5590	6.97
375	12096	10087	16.6
500	11065	10065	9.03
450	5908	4890	17.23
0	5906	**6907**	**-17.94**
300	6095	5076	16.71
500	6043	5003	17.2
500	6789	6007	11.51
0	7032	6790	3.44
350	6299	6100	3.15
200	5790	5004	13.57
50	6500	**6975**	**-7.3**
500	5788	4873	15.8
250	5891	5005	15.03
50	5901	4978	15.64
350	5740	4980	13.24
average 283.8095	**average 6998.524**	**average 6203.619**	**average 11.10429**

Table II

Average diuresis and median NTproBNP before and after dialysis in patients without changes of LVEF (group A)

Median diuresis (mL/day)	Predialysis median NTproBNP (pg/mL)	Postdialysis median NTproBNP (pg/mL)	Percentage of postdialysis changes of NTproBNP (%)
500	13872	9021	34.97
475	7021	4087	41.78
500	8050	4589	43.04
350	9005	5683	36.89
300	6609	4300	34.93
350	5802	3987	31.28
average 412.5	**average 8393.167**	**average 5277.833**	**average 37.14833**

Groups of patients	S_d	T	p
Type C vs Type N	26161	1.72	0.0980
Type N vs Type R	24646	1.41	0.1784
Type C vs Type R	31478	0.25	0.8080
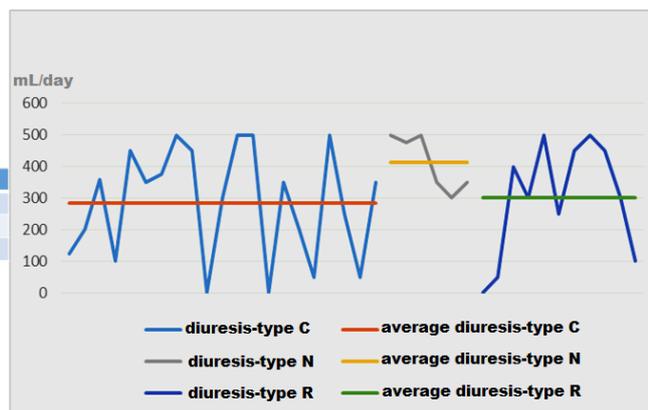
Figure 12.
Diuresis (mL/day) in relationship with the types of LVEF during dialysis in group A
Legends: C = cyclical pattern of LVEF changes; N = no significant LVEF changes; R = random modification of LVEF.

In the same time, statistical analysis showed, as seen also in Tables I and II, that the cyclical pattern of LVEF change after dialysis sessions was significantly correlated to the lowest diuresis (t test, p between < 0.00001 and 0.0003) (Figure 13). The average diuresis in patients with cyclical changes of LVEF was 283.80 mL/day compared to individuals without significant changes of LVEF that was 412.5 mL/day.

Groups of patients	S_d	T	p
Type C vs Type N	77	6.44	< 0.00001
Type N vs Type R	13	7.64	< 0.00001
Type C vs Type R	64	4.09	0.0003
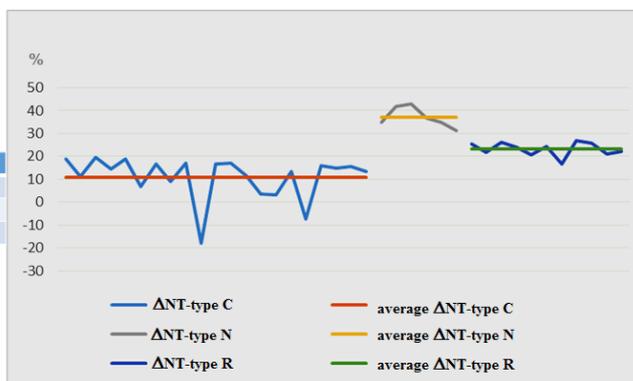
Figure 13.
The percentage changes of NTproBNP correlated to the cyclical pattern of LVEF during dialysis sessions
Legends: C = cyclical pattern of LVEF changes; N = no significant LVEF changes; R = random modification of LVEF; ΔNT = percentage change of NTproBNP.

In this study, we focused to highlight a significant link between residual diuresis and fluid status, dialysis UF, LVEF and cardiac biomarker NTproBNP in patients with more than 3 months history of chronic HD therapy (subjects without previous symptomatic cardiac disease).
The statistical analysis of our findings showed a gradually increasing incidence of hypervolemia with decreasing diuresis. This is expected if the patient has oliguria (in group A, an average of 90.31% of patients had hypervolemia before hemodialysis), but it is, obviously, an issue of noncompliance to the restriction of salt and water in patients with significant residual urine output (in group B, an average of 79.16%, and in group C an average of 34.02% of the patients had hyper-

volemia before dialysis). Additionally, the statistical analysis emphasized an inverse relationship between NTproBNP values before dialysis and diuresis; if we consider residual diuresis as a rough approximation of residual real function and that NTproBNP secretion increases with increasing plasma volume, these results are consistent with the literature data [14, 19, 28].

Instead, after hemodialysis, there was a clear and statistically significant predominance of hypo-volemia in group A: 58.99% *versus* 4.86% in group B and respectively 6.25% in the group C. This aspect, illustrated by the higher rate of UF in group A (average 5.08% of the dry weight compared with 2.81% of the dry weight in group B, and 0.94% in group C, respectively) is explained by the existence of a period of latency in filling the vascular bed from the interstitial and intracellular space in overhydrated patients.

Meanwhile, in group A, there was a significantly smaller decrease of NTproBNP levels after dialysis when compared with the other two groups (19.41% *versus* 39.89% in group B and 53.29% in group C), especially in patients with hypovolemia after dialysis sessions that is discordant with literature data about the increased secretion of NTproBNP in the presence of increasing myocardial stretch wall [14, 19, 20]. Failure of decreasing NTproBNP when the patient has become hypovolemic can be explained by the changes of LVEF after dialysis, highlighted in some patients from group A – those who have the lowest diuresis and smaller decreases in NTproBNP after dialysis (there is a cyclical decline and statistically significant, although temporary, of LVEF in these patients after each hemodialysis session). This finding can be explained as a phenomenon similar to the "stunned myocardium", originally described after myocardial infarction [29-32].

In chronic HD patients, the phenomenon of "stunned myocardium" has been previously described in the literature [33-37] and it was proved by various assessments: positron emission tomography, angiography, myocardial scintigraphy, serial echo-cardiography during dialysis [34, 37, 38]. Its aetiology is not fully elucidated [37, 38]. In some studies, endothelial dysfunction was considered the initial insult, ultimately leading to decreased coronary reserve [39, 40], as proven by the association with increased troponin levels [37, 41, 42]. Other researchers considered that the phenomenon of "stunned myocardium" during hemodialysis is a consequence of several metabolic disorders in HD population (e.g.: malnutrition, hypoalbuminemia, dialysis oxidative stress with release of oxygen radicals etc.) [40, 43]. The phenomenon has been also described in the absence of changes in angiography or troponin levels [34]. It was also observed in chronic HD children, highlighting a

possible genetic predisposition [44]. Links with high dialysis ultrafiltration volumes and/or dialysis hypotension has been also affirmed by some studies [40, 42]; instead, others have not found an association with ultrafiltration volume [45].

The importance of our research consists in emphasizing a cyclical decline of LVEF in a certain category of patients – individuals with very low values of residual diuresis who require considerable ultrafiltration volumes followed by hypovolemia after dialysis. In these patients, we found a significant correlation between the cyclical decline of LVEF and reduced fall of NTproBNP level after dialysis. We have not found any studies published in the literature that demonstrates the association between residual diuresis, changes in LVEF and NTproBNP. In overhydrated and oliguric HD patients, a gradual cardiac dilation may occur in the setting of hypervolemia; although volemia decreases after severe UF, the myocardium remains stunned for a period of time and the ejection fraction is reduced immediately after dialysis; as a consequence of persistent cardiac dilation, even in the presence of hypovolemia, myocardial wall NTproBNP secretion still continues. Depending on the individual myocardial and coronary reserves, there is a faster or slower recovery of systolic function, as proved in the current study by the lack of progressive increase of NTproBNP or permanent decrease in LVEF during the 3-months follow-up per patient. In the presence of the multiple cardiovascular risk factors in uraemia (e.g.: hypertension, inflammatory status, oxidative stress, dyslipidaemia, coronary vascular calcifications etc.), these, initially temporary, alterations in cardiac function may progress to cardiac failure [23].

It is important that this scenario occurred in oliguric patients, whose compliance in dietary restrictions is not sufficient to prevent large interdialysis weight increases. Since this complication did not occur in all oliguric patients, it is clear that there is individual variability. Therefore we consider that measuring NTproBNP variation before and after dialysis could be a useful marker for detecting patients at risk of developing early myocardial dysfunction.

Additionally to an adequate cardiovascular drug-therapy [46], such patients could benefit from changes in dialytic treatment: decrease of the dialysate temperature, lowering sodium in the dialysis solution, increasing the duration and frequency of hemo-dialysis sessions. Increased frequency and/or duration of the dialysis sessions is recorded to have the most favourable effect on the phenomenon of "stunned myocardium" and it fits the majority of patients.

The obvious limit of our study consists in the relatively small duration of patients' follow-up. Extensive researches for highlighting the relation-

ship between NTproBNP and long-term effects of cyclical intradialysis systolic dysfunction in oliguric patients at risk may be necessary in the future. Increased frequency and/or duration of HD sessions, contrary to the actual economic principles of a health system – which currently does not reimburse more than 3 sessions/week/patient – need a powerful scientific basis for implementation in clinical practice.

Conclusions

Our study highlights that in hemodialysis patients, reduced residual diuresis and high ultrafiltration volume were associated with increased values of NTproBNP both before and after dialysis and cyclical decrease of LVEF; thus oliguria may have deleterious long-term cardiac effects mediated by predialysis hypervolemia with repeatable increased cardiac wall stress and by postdialysis temporary, but cyclic, reduced inotropism. Further multicentre researches are needed to confirm these findings in larger cohorts of patients.

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