Associations Between Left Ventricular Hypertrophy and Hydration Status in Hemodialysis Patients

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Abstract. *Background and objective: Left ventricular hypertrophy (LVH) is a strong causal risk factor for cardiovascular morbidity and death in end-stage kidney failure. Fluid overload and hypertension are the major causes of left ventricular hypertrophy and failure. The aim of our study was to evaluate a relation between left ventricular hypertrophy in hemodialysis (HD) patients with cardiac biomarker NT-pro-BNP and hyperhydration measured by bioimpedance (BIA) and lung ultrasound (US).*

Materials and methods: We performed a one-center cross-sectional study of 36 patients undergoing chronic HD at the Hospital of the Lithuanian University of Health Sciences, Kaunas Clinics.

Echocardiography was conducted for all patients within 1 year before the beginning of the study. The criteria for LVH were left ventricular mass index (LVMI) > 115 g/m^2 in men and LVMI > 95 g/m^2 in women. The hydration level was evaluated using 2 methods: BIA and lung ultrasound (US). BIA, lung US and plasma NT-pro-BNP levels were tested during September and October 2014. BIA was performed after dialysis, and the volemia status was evaluated according to the ratio of extracellular (ECW) and total body water (TBW). Lung US was performed before and after hemodialysis in 8 points as described in the Blue protocol; extravascular lung water was estimated by calculation of B lines, i.e., the sum of B lines in all points was used in the final analysis.

Results: LVH was detected in 20 patients (56%). Patients with LVH were hyperhydrated on BIA measurement (ECW/TBW ratio 0.39 ± 0.013 vs 0.38 ± 0.01, P = 0.03). They had significantly more B lines on lung US before HD (4.55 ± 4.56 vs 1.94 ± 2.32, P = 0.045), and more than 3 times higher NT-pro-BNP levels before HD (14044.75 ± 10982.95 pg/mL vs 4116.21 ± 4399.42 pg/mL, P = 0.001) and after HD (13164.79 pg/mL ± 11073.65 pg/mL vs 3460.57 ± 4257.54 pg/mL, P = 0.002) as compared with patients without LVH. Patients with LVH also had higher systolic blood pressure before HD (149.22 ± 17.06 mmHg vs 134.11 ± 14.52 mm Hg, P = 0.02) and after dialysis (144.98 ± 17.16 mm Hg vs 127.61 ± 18 mm Hg, P = 0.015).

Conclusions: Left ventricular hypertrophy was present in more than half of prevalent hemodialysis patients. It was related to hyperhydration detected by bioimpedance and by lung ultrasound. In these patients the level of NT-pro-BNP before and after hemodialysis was more than 3 times higher as compared with those without left ventricular hypertrophy. Further studies are needed for confirmation of causal relation of these associations.

Introduction

The heart and the vascular tree undergo major structural and functional changes when kidney function declines and renal replacement therapy is required. In end-stage kidney disease patients, the vascular tree can be affected by both atherosclerosis and arteriosclerosis with lipid rich plaques and abundant media calcification. The many cardiovascular risk factors and adaptive changes the heart undergoes include left ventricular hypertrophy (LVH) and dilatation with concomitant systolic and diastolic dysfunction. Myocardial fibrosis is the consequence of impaired angio-adaptation, reduced capillary angiogenesis, myocyte-capillary mismatch, and myocardial micro-arteriopathy.

Fluid overload and hypertension are the major causes of left ventricular hypertrophy and failure. They may directly affect myocardial function [1]. The most frequent cause of hypertension in hemodialysis patients is volume overload, which is associated with poor cardiovascular outcomes itself independent of blood pressure. Extracellular volume reduction by persistent ultrafiltration and dietary salt restriction can produce favorable results with good blood pressure control [2]. Debates continue for which volume status evaluation method is most appropriate for use in clinical practice. There are data that bioimpedance-based fluid management

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may reduce left ventricular mass in hemodialysis patients [3]. However, there are controversial data showing that left ventricle hypertrophy was not directly related to the hydration status [4]. The search for specific biomarkers is also an aim of many studies. The relationship of cardiac biomarkers with LVH in asymptomatic patients undergoing hemodialysis treatment has been described in literature [5, 6].

The aim of our study was to evaluate the relation of left ventricular hypertrophy in hemodialysis patients with cardiac biomarker NT-pro-BNP and hyperhydration measured by bioimpedance (BIA) and lung ultrasound (US).

Methods

We performed a one-center cross-sectional study of 36 patients undergoing chronic HD at the Hospital of the Lithuanian University of Health Sciences Kauno Klinikos. All study patients were older than 18 years with hemodialysis vintage at least 3 months. All patients were on hemodialysis thrice a week for 4 hours using synthetic or semisynthetic dialysis membranes, reverse osmosis purified water, and bicarbonate-base hemodialysis solution. The exclusion criteria were any respiratory illness or pulmonary infection (bias for lung US), big metal prosthesis, and an electrocardiostimulator (bias for BIA).

The study was approved by Kaunas Regional Biomedical Research Ethics Committee (protocol No. BE-10-2), and Center of Bioethics of the Lithuanian University of Health Sciences (BEC-LMB(M)-192).

Echocardiography was conducted for all the enrolled patients within 1 year before the beginning of the study. Left ventricular mass was corrected for body surface area and presented as left ventricular mass index (LVMI). The criteria for LVH were LVMI > 115 g/m^2 in men and LVMI > 95 g/m^2 in women [7].

The hydration level was evaluated using 2 methods: BIA and lung ultrasound (US) for detection of extravascular lung water. BIA, lung US and plasma NT-pro-BNP levels were tested during September and October 2014. Then, the patients were followed until May 2017 for survival.

Bioimpedance analysis was performed using InBody S10, Biospace Co., Ltd. (Korea) 20 minutes after hemodialysis (HD). The volemia status was evaluated according to the ratio of extracellular (ECW) and total body water (TBW), and fluid overload was considered as ECW/TBW ratio being higher than 39%.

All the patients were evaluated at the bedside for weight and blood pressure before and after dialysis 3 times: on the day of lung US, BIA performance, and NT-pro-BNP testing. The mean of these 3 measurements was included into statistical analysis.

Blood samples for NT-pro-BNP testing were collected into the vacutainers with EDTA immediately before and after HD. Testing was performed by chemiluminescent analysis using polyclonal antibodies.

Lung US was performed before and after hemodialysis by one trained doctor with a standard transducer. The participants were examined in the sitting position and both lungs were scanned. Each hemithorax was examined from apex to base in 4 points as described in the Blue protocol [8]: two points on the anterior chest, one point on the lateral chest, and an additional point on the posterobasal subscapular. Extravascular lung water was estimated by calculation of B lines – hyperechoic reverberation artifacts between thickened septa and the overlying pleura that are defined as "lung comets". The sum of B lines in all 8 points was used in the final analysis.

Variables were expressed as frequencies, percentages for discrete factors and mean values ± standard deviation (SD) for continuous factors. Statistical analysis was performed using SPSS packages. The Student *t* test and the Mann-Whitney-Wilcoxon test were used for comparison of continuous variables. The Pearson chi-Sqare test was used for comparison of categorical variables. The association between two continuous variables was evaluated by calculating the Pearson correlation coefficient. Statistical significance was assumed at $P < 0.05$.

Results

At the beginning of the study (September 2014), we included 36 ambulatory hemodialysis patients, 12 woman and 24 men, who agreed to participate in the study, and underwent all required tests (heart ultrasound, lung ultrasound, bioimpedance analysis and NT-pro-BNP testing). During the study period (May 2017), 5 patients died, 9 patients were transplanted and 22 patients remained on hemodialysis. LVH was detected in 20 patients (56%). The mean ventricular mass index was 127.3 ± 27.2 g/m^2 in men and 96.02 ± 26.2 g/m^2 in women. Nine patients (25%) had heart ejection fraction lower than 50%. Fluid overload was found in 9 patients (25%) after hemodialysis. Other measured parameters are shown in Table 1.

Table 1. Patients' (n=36) Characteristics

Factor	Mean	Standard Deviation
Age, years	58.75	14.02
ECW/TBW ratio	0.39	0.012
BMI kg/m^2	24.50	4.77
Ejection fraction %	51.75	8.97
Sum of B lines before HD	3.39	3.92
Sum of B lines after HD	1.58	3.16
NT-pro-BNP before HD, pg/mL	9956.53	10083.43
NT-pro-BNP after HD, pg/mL	9047.85	10003.11
Systolic BP before HD, mm Hg	142.75	17.483
Diastolic BP before HD, mm Hg	80.62	9.42
Systolic BP after HD, mm Hg	137.54	19.30
Diastolic BP after HD, mm Hg	80.61	10.30

BMI, body mass index; ECW/TBW, extracellular water/total body water; BP, blood pressure.

Table 2. Comparison of Hemodialysis Patients According to Left Ventricular Mass

Factor	Without LVH (n=16)	LVH (n=20)	*P*
Age, years	60.68 ± 11.08	57.46 ± 15.86	0.5
ECW/TBW ratio	0.38 ± 0.01	0.39 ± 0.013	**0.03**
BMI kg/m2	24.0 ± 4.0	24.86 ± 5.32	0.6
Ejection fraction %	53.31 ± 5.5	50.50 ± 10.99	0.36
Sum of B lines before HD	1.94 ± 2.32	4.55 ± 4.56	**0.045**
Sum of B lines after HD	0.69 ± 0.95	2.3 ± 4.05	0.1
NT-pro-BNP before HD, pg/ml	4116.21 ± 4399.42	14044.75 ± 10982.95	**0.001**
NT-pro-BNP after HD, pg/ml	3460.57 ± 4257.54	13164.79 ± 11073.65	**0.002**
Systolic BP before HD, mm Hg	134.11 ± 14.52	149.22 ± 17.06	**0.02**
Diastolic BP before HD, mm Hg	78.81 ± 8.42	81.98 ± 10.16	0.4
Systolic BP after HD, mm Hg	127.61 ± 1801	144.98 ± 17.16	**0.015**
Diastolic BP after HD, mm Hg	77.44 ± 8.68	82.98 ± 11.04	0.2

LVH, left ventricular hypertrophy; BMI, body mass index; ECW/TBW, extracellular water/total body water; BP, blood pressure.

All the patients were divided into 2 groups according to LVMI measured by heart ultrasound: LVH and without LVH. Differences between the groups are shown in Table 2.

The patients with LVH were hyperhydrated on BIA measurement. They had significantly more B lines on lung US before HD and more than 3 times higher NT-proBNP levels before and after HD as compared with the patients without LVH. The patients with LVH also had higher systolic blood pressure before and after dialysis.

Some patients (40%) with LVH had volume overload (ECW/TBW > 0.39) as compared with 7% in the group without LVH ($P = 0.03$). Examination of hyperhydrated HD patients revealed that 89% of them had LVH as compared with only 48% in the group without LVH.

The correlation analysis between our tested parameters is shown in Table 3.

LVMI had a significant moderate positive correlation with the ECW/TBW ratio, measured by BIA, the plasma NT-pro-BNP level before and after dialysis, and the sum of B lines before and after HD measured by the lung US.

All 5 patients who died had LVH. Distributions of LVMI in different outcome groups are shown in Table 4.

Table 4. Mean of Left Ventricular Mass Index According to Outcomes of HD Patients

Outcome	n	Mean ± SD
Patients who died	5	143.9 ± 17.4 g/m^2
Transplanted patients	9	98.2 ± 30.8 g/m^2
Patients remaining on HD	22	118.4 ± 28.3 g/m^2

$P = 0.02$.

Table 3. Correlation Between LVMI, B Lines, ECW/TBW Ratio and NT-proBNP in Hemodialysis Patients

Factor		ECW/TB ratio	B lines after HD	B lines before HD	NT-pro-BNP before HD	NT-pro-BNP after HD	LVMI g/m^2
ECW/TBW ratio	Pearson correlation	1	0.308	0.213	0.499	0.545	0.554
	P		0.077	0.226	**0.004**	**0.002**	**0.001**
B lines after HD	Pearson correlation	0.308	1	0.317	0.210	0.246	0.360
	P	0.077		0.059	0.234	0.168	**0.031**
B lines before HD	Pearson correlation	0.213	0.317	1	0.188	0.258	0.379
	P	0.226	0.059		0.287	0.147	**0.023**
NT-pro-BNP before HD, pg/ml	Pearson correlation	0.499	0.210	0.188	1	0.995	0.538
	P	**0.004**	0.234	0.287		0.000	0.001
NT-pro-BNP after HD, pg/mL	Pearson correlation	0.545	0.246	0.258	0.995	1	0.574
	P	**0.002**	0.168	0.147	**0.000**		0.000
LVMI g/m^2	Pearson correlation	0.554	0.360	0.379	0.538	0.574	1
	P	0.001	0.031	0.023	0.001	0.000	

ECW/TBW ratio, ratio of extracellular and total body water; LVMI, left ventricular mass index.

Discussion

Our study found a significant relation between left ventricular hypertrophy and hyperhydration measured by different methods: bioimpedance, lung ultrasound, and pro-BNP.

LVH is present in 68–89% of incident hemodialysis patients and is frequently progressive, although regression is observed in a minority of patients [5], [9, 10]. In our study, we found LVH in more than half of prevalent HD patients (56%). Although clinical diagnosis of hypertensive cardiomyopathy made by a doctor-practitioner was found in nearly 90% of patients (this was not shown in results), this number reduced according to a LVMI calculation from recent heart ultrasound. We may speculate that with implementation of new volume assessment methods we may reach better volume control and less hypervolemia, as well as possible regression of LVH in some patients, but this was not confirmed in our study.

Left ventricular hypertrophy is a strong causal risk factor for cardiovascular morbidity and death in end-stage kidney failure. While left ventricular hypertrophy remains a fundamental treatment target in end-stage kidney failure, the measurement of left ventricular mass index (LVMI) solely for risk stratification is unwarranted in this condition [11]. Hyperhydration, including lung congestion, increased cardiac biomarkers, and hypertension are also related to worse survival of hemodialysis patients [12–15].

There are different methods for evaluation of volemia, each of them having advantages and drawbacks. The gold standard is the measurement by radioimmunoassay, but this technique cannot be used in clinical practice. Chest X-ray is limited due to the radiation exposure and the large interobserver variation. Other technologies promise rapid and accurate evaluation of the hydration status, including bioelectrical impedance analysis, and detection of lung comets by chest US [16]. Hyperhydration detected by both of these methods had relation to LVH in our study.

We have been routinely performing bioimpedance analysis in all our dialysis patients since 2013 in our Hospital of the Lithuanian University of Health Sciences Kauno Klinikos. We perform BIA after dialysis in order to detect constant hypervolemia in between dialysis; we believe that we can better control "dry" weight in such management. We found a moderate positive correlation of the ECW/TBW ratio and LVMI; HD patients with LVH were more hyperhydrated. Although LVH is related to volume overload, not all clinical studies could confirm this relation using BIA. Authors from Madrid have found that left atrial volume index determined by the echo-cardiographic area-length method, but not left ventricle hypertrophy or dimensions of cavities, is related to the hydration status based on bioimpedance measured time-averaged fluid overload [4].

Bioimpedance analysis method is easy to perform and may be done by trained dialysis nurses, but it is still not perfect. Thus, we started to implement other methods described in literature – lung US and measurement NT-pro-BNP - from the year 2014. The main drawback of the lung US test is that it needs experience and cannot be done by a dialysis nurse or not trained nephrologist. We used the previously described Blue protocol [8] as the basis for our testing; as we could perform lung US in the sitting position, it was easier for us to test not only 3 main points described (two points on the anterior chest, one point on the lateral chest), but also an additional – posterobasal subscapular – point, which was used instead of the lateral chest point in some protocols. We used a sum of B lines from all the points in our analysis. Some authors propose to use lung US as the best method for volume assessment. They confirm that the lung comet score is the best predictor for the relationship hydration status – mortality, independent of bioimpedance-derived parameters [14]. In another study, lung water excess was unrelated to the hydration status but it was strongly associated with New York Heart Association functional class, left ventricular ejection fraction, early filling to early diastolic mitral annular velocity, left atrial volume, pulmonary pressure, and also with LVMI. In a multiple regression model including traditional and nontraditional risk factors, only left ventricular ejection fraction maintained an independent link with lung water excess [17]. We also found a positive relation between the sum of B lines and LVH and no direct correlation with the ECW/TBW ratio and NT-pro-BNP levels. These data need to be confirmed in bigger studies.

ECW expansion as determined by BIA or lung US may not equate with plasma volume expansion. As such, simple reliance on single BIA or lung US assessments of ECW volume without clinical review may lead to inappropriate management decisions. Combining other methods of volume assessment with biomarkers of plasma volume and cardiac function may prove helpful in aiding the clinical assessment of target weight. For cardiac biomarkers we chose to use NT-pro-BNP as it is more stable than BNP [13]. In our study, pro-BNP before and after HD correlated with hyperhydration measured by BIA, but not with lung ultrasound. As a biomarker, NT-pro-BNP, whether it signifies underlying cardiac disease, vascular leak secondary to inflammatory conditions, or simple overhydration, is highly associated with mortality. However, studies designed to assess whether these cardiac peptide hormones can aid in determining "dry" or target weight for hemodialysis patients have failed to establish a role in clinical practice. On the other hand, it is more likely that as many hemodialysis patients have left ventricular hypertrophy, individual patients will have their own optimum range for NT-pro-BNP when at their "dry" or target weight, and as such there is currently no established "normal" range for BNP to allow clinical decisions that postdialysis target weights should be increased or decreased [18]. Our results also show a

wide range of pro-BNP concentrations in hemodialysis patients: from 507 pg/mL before HD, and 301 pg/mL after HD to more than 30000 pg/mL.

The diagnostic and prognostic cut-off values for NT-pro-BNP in ESRD are significantly elevated compared with the cut-off values in patients with none or mildly impaired renal function. For example, in hemodialysis patients, an NT-pro-BNP cut-off value $\geqslant$ 7200 ng/L could discriminate patients with left ventricular disease from those without. In our study, we also found a very high mean level of NT-pro-BNP, > 9000 pg/mL, both before and after dialysis. There are suggestions that not only glomerular filtration rate level but also the dialysis process itself may influence BNP and NT-pro-BNP concentrations, like the type of dialysis membrane. Interestingly, some find elevated levels of NT-pro-BNP after dialysis whereas others find lower values. In our study, we found a reduction of NT-pro-BNP levels after HD. Other parameters related to the dialysis treatment, such as a patient's volume status, could also affect NT-pro-BNP concentrations whereby an increase in extracellular volume might induce left ventricular dilatation and subsequent increases in NT-pro-BNP concentrations [13]. We found a very clear difference between mean NT-pro-BNP levels and LVH: 14044.75 pg/mL in the LVH group and 1446.21 pg/mL in the group without LVH before dialysis and a slightly lower concentration but the same difference after dialysis. We confirmed data of other studies about a moderate positive correlation between NT-pro-BNP and LVH [5].

In our study, the levels of NT-pro-BNP correlated with the ECW/TBW ratio, but not with the sum of B lines before and after dialysis.

We also found a relation between LVH and higher systolic BP before and after dialysis. Some studies showed that higher systolic, and diastolic as well, or pulse pressure, regardless of timing with dialysis, were associated with higher LV mass [19]. We did not find any relation between LVH and diastolic BP in our study. Future studies should consider the use of various BP measures in examining the impact of BP on LVM and cardiovascular disease. Findings from such studies could suggest that high BP should be more aggressively treated to promote LVH regression in incident hemodialysis patients [19].

Conclusions

Left ventricular hypertrophy was present in more than half of prevalent hemodialysis patients. It was related to hyperhydration detected by bioimpedance and by lung ultrasound. In these patients the level of NT-pro-BNP before and after hemodialysis was more than 3 times higher as compared with those without left ventricular hypertrophy. Further studies are needed for confirmation of causal relation of these associations.

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