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Impact of active fluid management on cardiac hemodynamics and mechanics in patients on maintenance hemodialysis

Uticaj aktivne kontrole volemije na srčanu hemodinamiku i mehaniku kod bolesnika na hroničnom lečenju hemodijalizom

Zoran Paunić*, Milica Dekleva-Manojlović†, Nataša Marković-Nikolić†, Nemanja Rančić‡, Nada Dimković§

***Special Hospital for Hemodialysis "Fresenius Medical Care", Belgrade, Serbia; Zvezdara University Medical Center, †Clinical Department for Cardiovascular Diseases, §Clinical Department for Renal Diseases, Belgrade, Serbia; University of Defence, ‡Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia**

Abstract

Background/Aim. Overhydration (OH) and shortcomings of clinical assessment of so called „dry weight" in hemodialysis (HD) patients are well known risk factors for high cardiovascular morbidity and mortality in this population. The purpose of this prospective randomized study was to investigate possible benefits of the active fluid management (AFM) guided by bioimpedance spectroscopy (BIS) on cardiac morphology, mechanics and function in chronic hemodialysis patients. **Methods.** The study lasted 9 months and 83 BIS naive patients were enrolled. Cardiac structural and functional characteristics were obtained using two dimensional Doppler echocardiography and global strains by speckle tracking modality. In addition, cardiac markers were measured. **Results.** Seventy three patients completed the study (38 in the active – AFM group and 35 in the control group). At the end of the study, the main structural change in the active group of patients was reduction of left ventricular mass index (from 62.81 ± 19.74 g/m$^{2.7}$ to 57.74 ± 16.87g/m$^{2.7}$; $p = 0.007$), while main functional improvements in this group were better left ventricular ejection fraction (LVEF; from 41.27 ± 9.26% to 43.95 ± 8.84%; $p = 0.006$) and fractional shortening (FS; 27.86 ± 5.94% to 29.86 ± 5.83%; $p = 0.056$) in accordance with improvement of radial left ventricular (LV) mechanics detected by higher global radial strain (GRS) (18.56 ± 10.24% to 21.79 ± 12.16%; $p = 0.014$). The diastolic function of patients in the control group worsened significantly, assessed as ratio of Doppler velocity of early diastolic filling of left ventricle – E, and average velocity of tissue Doppler measured at lateral part of the mitral annulus (e' lateral; E/e' lateral ratio 10.59 ± 5.00 to 11.12 ± 4.06; $p = 0.036$) and consecutively the right ventricular systolic pressure (RVSP) estimated indirectly by echocardiography: from 34.84 ± 10.18 mmHg to 38.76 ± 8.34 mmHg; $p = 0.028$. These functional changes were in correlation with significantly higher levels of N-terminal prohormone brain natriuretic peptide (NT-proBNP) in this group of patients [median and interquartile range (IQR): 5810.0 pg/mL (3339.0–15627.0 pg/mL) to 8024.0 pg/mL (4433.0–17467.0 pg/mL; $p = 0.038$)]. The improvement in the LV structure and function in the active group correlated with better relative overhydration (ROH) management in this group – the proportion of "critically" overhydrated patients decreased from 45% at the start to 24% at the end of study ($p = 0.003$). At the end of the study, there were 49% of post-dialysis "critically" dehydrated patients in the control group. Proportion of anuric patients increased only in the control group (63% to 77%; $p = 0.063$). **Conclusion.** Active fluid management, guided by bioimpedance spectroscopy had positive impact on cardiac hemodynamics and mechanics in our study patients and could improve clinical decisions regarding their optimal weight and further clinical course. Further data from well designed studies are needed urgently.

Key words:
renal dialysis; ventricular function, left; echocardiography, doppler; biolectric impedance; biomarkers.

Apstrakt

Uvod/Cilj. Hipervolemija i nedostaci kliničkog procenjivanja tzv. „suve težine" kod bolesnika na lečenju hemodijalizom (HD) su dobro poznati faktori rizika za visok kardiovaskularni morbiditet i mortalitet ove populacije. **Metode.** Sprovedena je unicentrična, randomizirana prospektivna studija da bi se ispitala moguca korist primene aktivne kon-

Correspondence to: Zoran Paunić, Special Hospital for Hemodialysis "Fresenius Medical Care", Dragačevska 11, 11 000 Belgrade, Serbia. E-mail: zoran.paunic@gmail.com

trole volemije (AKV), a na osnovu njenog merenja bioimpedantnom spektroskopijom (BIS), na srčanu morfologiju i funkciju i na miokardnu mehaniku kod hroničnih HD bolesnika. U studiji je učestvovalo 83 HD bolesnika kojima nikada ranije nije rađeno merenje volemije BIS-om i studija je trajala devet meseci. Srčana struktura i funkcionalne karakteristike procenjivane su dvodimenzionalnom Dopler ehokardiografijom, a globalno naprezanje *speckle-tracking* modalitetom. Određivani su nivoi kardioloških markera u krvi. **Rezultati.** Studiju je završilo 73 bolesnika (38 u aktivnoj – AKV grupi i 35 u kontrolnoj grupi). Na kraju studije, glavna strukturna promena u aktivnoj grupi bolesnika bila je redukcija indeksa mase leve komore (62,81 ± 19,74 g/m^{2,7} na početku studije i 57,74 ± 16,87 g/m^{2,7} na kraju studije, $p = 0,007$), dok su glavna funkcionalna poboljšanja u ovoj grupi bolesnika bila poboljšanje ejekcione frakcije leve komore (LVEF, sa 41,27 ± 9,26% na 43,95 ± 8,84%, $p = 0,006$) i njenog frakcionog skraćenja (FS; 27,86 ± 5,94% do 29,86 ± 5,83%, $p = 0,056$), u skladu sa poboljšanjem radijalne mehanike miokarda leve komore registrovanog višim globalnim radijalnim naprezanjem (*strain*-om) (GRS) na kraju studije (18,56 ± 10,24% do 21,79 ± 12,16%, $p = 0,014$). Bolesnici u kontrolnoj grupi imali su značajno pogoršanje dijastolne funkcije procenjeno na osnovu porasta odnosa Doplera brzine ranog dijastolnog punjenja leve komore – E i srednje brzine tkivnog Doplera lateralnog dela mitralnog anulusa – e' (E/e' lateralno; 10,59 ± 5,00 do 11,12 ± 4,06; $p = 0,036$) i posledično, povišenim sistolnim pritiskom u desnoj komori (SPDK, od 34,84 ± 10,18 mmHg do 38,76 ± 8,34 mmHg; $p = 0,028$). Ove funkcionalne promene kod bolesnika u kontrolnoj grupi korelirale su sa značajnim pogoršanjem nivoa N-terminalnog prohormona moždanog natriuretskog peptida (NT-proBNP): medijana i interkvartalni rasopon (IQR) od 5810,0 pg/mL (3339,0–15627,0 pg/mL) na početku studije do 8024,0 pg/mL (4433,0–17467,0 pg/mL; $p = 0,038$), na kraju studije. Poboljšanje srčane morfologije i funkcije u aktivnoj grupi korelirao je sa značajnim smanjenjem procenta „kritično" hipervolemičnih bolesnika na kraju studije (sa 45% na 24%; $p = 0,003$). Na kraju studije, postdijalizno „kritično" dehidriranih bolesnika u kontrolnoj grupi bilo je 49%. Procenat anuričnih bolesnika porastao je samo u ovoj grupi, sa 63% na 77% ($p = 0,063$). **Zaključak.** Koncept aktivne kontrole volemije vođene bioimpedantnom spektroskopijom pozitivno je uticao na hemodinamiku i mehaniku srca kod bolesnika na hroničnom lečenju hemodijalizom i može da pomogne u kliničkom određivanju njihove optimalne težine i daljem kliničkom toku. Potrebni su što pre dodatni podaci o ovom problemu iz dobro dizajniranih studija.

Ključne reči:
dijaliza; funkcija leve komore; ehokardiografija, dopler; bioelektrična impedanca; biomarkeri.

Introduction

The left ventricular myocardial hypertrophy (LVH) and diastolic dysfunction (DD) are dominant cardiac disorders seen in dialysis patients with prevalence 60% to 80% [1–5]. Both disorders are the consequence of hemodynamic (increased preload and afterload) and non-hemodynamic mechanisms (oxidative stress, inflammation, mineral metabolism disturbance etc.) [6, 7]. However, there is still a paradigm that hypervolemia or overhydration (OH) is the main contributing factor for higher blood pressure, LVH and DD among chronic dialysis patients. The main causes of hypervolemia in hemodialysis (HD) patients are oligoanuria, patients' non-compliance and the intermittent nature of HD procedure. There is general consensus that better control of dry weight (DW) in HD patients leads to improved control of hypertension and to left ventricular (LV) mass regression/LV volumes reduction [8–11].

Despite a plethora of methods that have been applied such as measuring inferior vena cava diameter, determination of natriuretic peptides blood level, blood volume monitoring, there is still no ideal and practical method for determining DW [12, 13] and it relies often on conventional clinical assessment [14–16]. Nevertheless, the clinical assessment, alhough rapid and easily applies at the bedside, has its disadvantages [17–20]. There is a growing evidence that bioimpedance spectroscopy (BIS) gives reliable information about OH in dialysis patients [21–27] and correlates well with left ventricular mass (LVM) and cardiomarkers [28]. According to some reports, better control of extracellular water (ECW) by BIS could lead to improved control of arterial hypertension in HD patients [19, 29, 30] and even better management of left ventricular mass in comparison to the standard clinical approach [28, 31]. Still, there are no prospective randomized studies about influence of BIS guided volume control on diastolic function, myocardium mechanical and contractile features in addition to heart morphology and cardiac biomarkers.

The purpose of this prospective randomized study was to investigate possible benefits of the active fluid management (AFM) guided by BIS on cardiac morphology, mechanics and function in chronic hemodialysis patients.

Methods

Study population

This single center, prospective, randomized study included 136 patients on regular HD in the Dialysis Unit of Zvezdara University Medical Center in Belgrade, during the period from February 2013 to August 2014. The study protocol was approved by the Ethical Committees of the Faculty of Medicine, University of Belgrade and the Zvezdara University Medical Center. All participants gave written informed consent to participate in the study. A study schema is presented in Figure 1. From the patients screened, 83 patients fulfilled inclusion/exclusion criteria and were enrolled in the study. The randomization 1 : 1 was made by using online program available at URL http:/www.graphpad.com/quickcalcs/randomize1.cfm and patients were randomized either to the active (n = 42) or to the control group (n = 41). Nine months after enrollment in the study, 38 patients from the active and 35 patients from the control group completed the study.

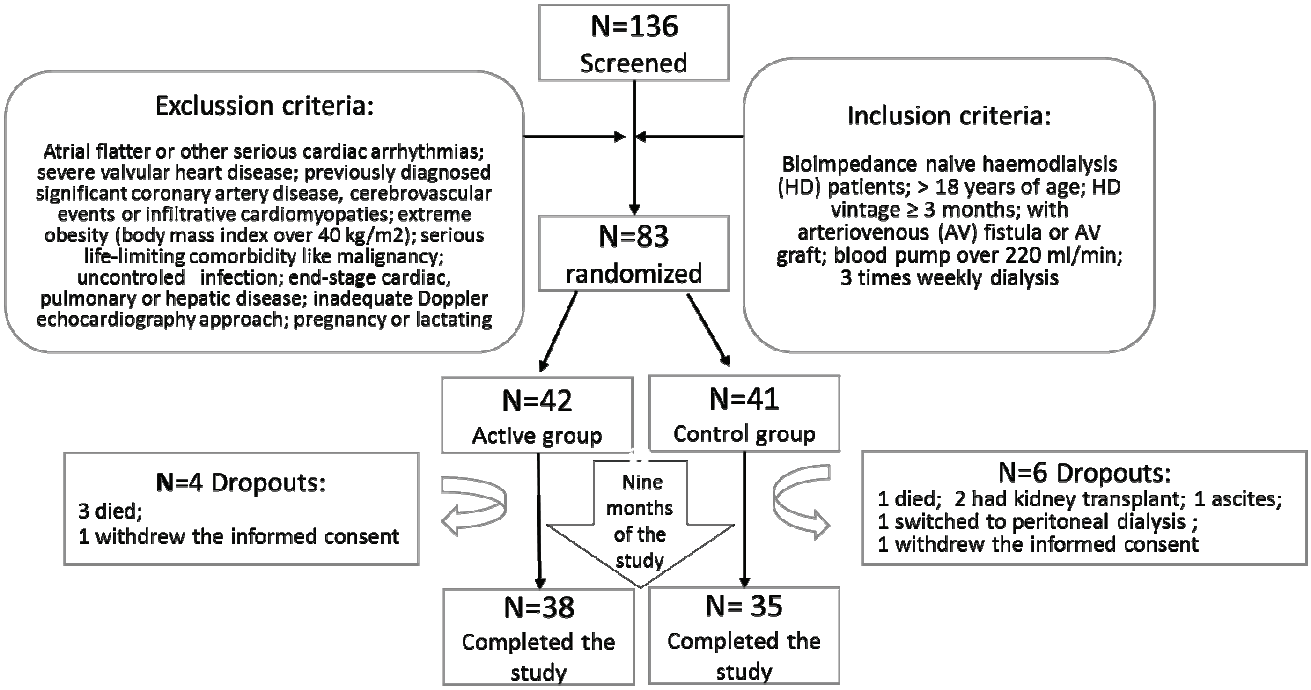

Fig. 1 – Exclusion and inclusion criteria and the study scheme.

Determination of hydration and concept of active fluid management

Hydration status was determined by BIS method implemented in the Body Composition Monitor (BCM, Fresenius Medical Care, Germany). The principles of the technique, validation and clinical implementation have been described elsewhere [18–22, 32]. Volemia is determined by using a physiologic model as a model of normal tissue hydration [22]. The BCM gives OH in liters and suggestion of normal weight (NW) for any particular patient. As well as the determination of OH, the BCM provides information about adipose tissue mass (ATM) and lean tissue mass (LTM). The BCM is routinely used for assessing body composition in many dialysis centers [26, 27].

To overcome the problem of measuring hydration on different sessions of the week which generally results in different OH levels, the concept of average weekly OH (AWOH) was introduced. The basic assumption for application of AWOH is that ATM and LTM remain constant over the period of a week. In the case of thrice weekly HD, only one BCM measurement on any session day of the week is needed. The remaining two OH values are calculated from pre-dialysis weights (preHD_W) and NW:

$OH_{D-1} = preHD\_W_{D-1} - NW$;

$OH_{D-2} = preHD\_W_{D-2} - NW$;

where D-1 and D-2 stands for dialysis sessions prior to dialysis (D) when BCM measurement was conducted.

AWOH is then equal to $(OH_{D-2} + OH_{D-1} + OH_D)/3$

The AWOH was then normalized to ECW to cater for subjects of differing weight and body composition.

Average weekly relative OH (Av_ROH):AWOH/ECW is given in percentage.

Post-dialysis over- or underhydration (postOH) was calculated from post-dialysis weight measurements:

postOH = NW-Weight after dialysis session

Average relative postOH (Av_postROH) was then:

$(OH_{D-2} + OH_{D-1} + OH_D)/3$*ECW (in percentage).

An AFM process was devised for application in those patients enrolled in the active group. This process aims to maintain the pre-dialysis Av-ROH in active patients below 15% as this threshold was considered critical for increased risk of cardiovascular morbidity and mortality in the HD population [18, 33]. A post Av-ROH of -6% was applied to limit dehydration based on previous studies in order to avoid patients' simptoms of dehydration, lower quality of life and to preserve their residual renal function [18, 31, 34, 35], although firmer evidence for this threshold is lacking.

The AFM concept summary and algorithm are provided in Figure 2.

The implementation of active fluid management and body composition monitor

After BCM measurement, in the active group, DW was targeted according to the AFM algorithm and clinical judgment. In the control group, DW was determined only according to routine clinical assessment. The BCM measurements were also performed in this group, but the results remained blinded to the responsible physician.

The BCM measurement was undertaken prior to the start of dialysis treatment, by trained nurses. In the active study group, BCM was performed weekly or monthly, based on the flowchart in Figure 2. In the control group, BCM was performed monthly. Blood pressure (BP) was taken manually before the connection on HD and after the HD session, in the recumbent position.

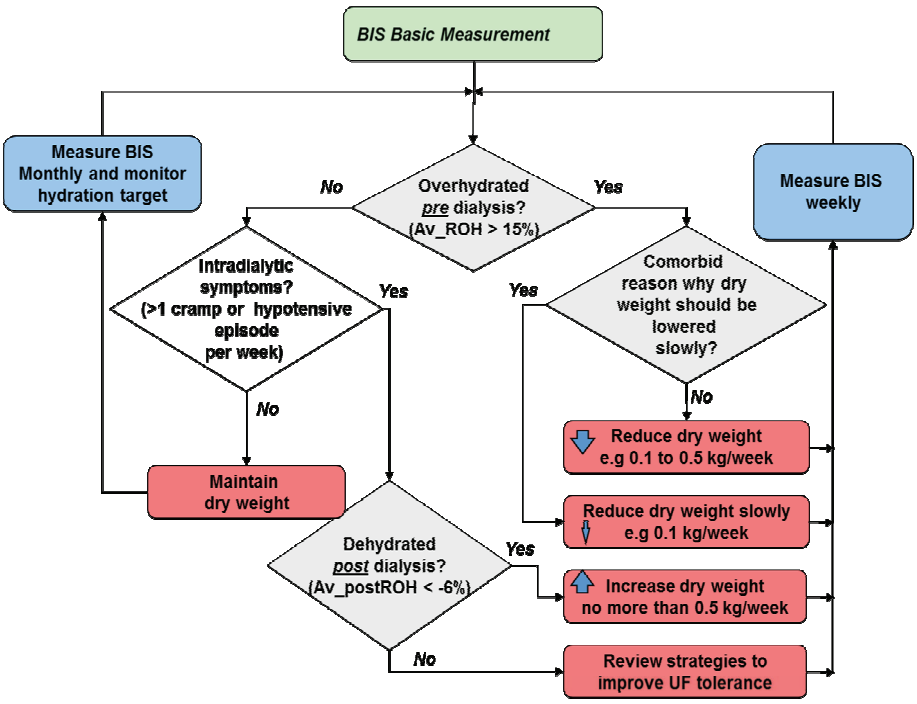

Fig. 2 – Active fluid management flowchart.
BIS – bioimpedance spectroscopy; Av_ROH – average weekly relative overhydration (OH); Av_postROH – average relative post-dialysis over- or underhydration; UF – ultrafiltration.

The mean value of BP measurements at time of BCM and five treatments before BCM were calculated for subsequent analysis. Weight gain was measured as the difference between pre-dialysis weight and clinically targeted patient's DW. An average of three weekly weight gains were divided by the DW as a relative average weight gain (WG_Av) and recorded as a percentage value.

Echocardiography

The echocardiographic examinations at the start and at the end of the study (i.e. 9 months after enrollment) were performed in all patients one day after dialysis in order to avoid the impact of ultrafiltration or pre-dialysis fluid on these measurements, as recommended [36].

The examinations were performed by a cardiologist who had no knowledge to which group (active of control) patients were enrolled. The assessment was done using Toshiba ARTIDA Aplio Ultrasound Machine using 2–4.2 MHz phase array probe for cardiac study in accordance with the recommendations of the European and American Society of Echocardiography [37].

Using M mode images, LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were obtained as well as intraventricular septum thickness (IVST) and posterior wall thickness (PWT). Relative wall thickness (RTW) was calculated by the standard formula RWT = 2 PWT/LVEDD. Left ventricular volumes (LVEDV and LVESV) were measured using the modified Simpson's method from the apical 4 - and 2-chamber views and indexed by body surface area (BSA) (LVEDVI and LVESVI) and ejection fraction was calculated (LVEF). The similar method, the apical 4 - and 2-chamber endocardial tracing was used for the calculation of the left atrial volume (LAV) and LAV indexed by BSA (LAVI) [37]. LVEF was considered normal if it was ≥ 50% [38].

Left ventricular mass (LVM) was calculated using the Devereux formula[39] and indexed by BSA (LVMI) and by height (h) raised to an exponential power of 2.7 ($LVMI^{2.7} = LVM/h^{2.7}$) [2, 40]. The LVH was defined on the basis of $LVMI^{2.7}$ greater than 48 g/m $^{2.7}$ for men and 44g/m$^{2.7}$ for women [17]. The changes in LVM were also observed. A change greater than 5% of $LVMI^{2.7}$ at the end of the study was considered clinically significant.

Parameters of LV diastolic functions were: peak early (Vmax E), late (Vmax A), and annularlateral and medial e' wave velocity (e' lat and e' med respectively) as well as E/A ratio and E/e' ratio. The parameter E/e' ratio was interpreted as an indirect measure of left ventricular end-diastolic pressure.

The following criteria were applied for the identification of diastolic dysfunction (adapted from Pecois-Filho [7]: E/A ratio < 0.8 or > 2; e' ≥ 8 cm/s; average E/e' ≥ 8; LAVindex > 34 mL/m^2). For the assessment of the structural and functional performance of the right ventricle (RV), the following measurements were used: RV dimension at 4 chamber view, tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic pressure (RVSP), and tricuspid regurgitation [37].

The additional measurement of inferior vena cava (IVC) antero-posterior diameter was performed at the end of the echocardiographic examination in supine position from sub-costal approach within 2.5 cm of IVC - right atrium junction, during unforced breathing. From the recorded frames loops, passive maximal (IVCmax) and minimal IVC

diameter (IVCmin) were obtained (i.e. without sniffing, in order to avoid differences in the magnitude of the inspiratory effort which can influence IVC collapsibility) [41, 42].

The indexed IVCi was calculated by dividing the IVCmax (in mm) by the BSA (in m^2). The IVC collapsibility index (IVC-CI; in %) was calculated by using the following standard formula: [(IVCmax − IVCmin)/IVCmax] × 100.

*Two dimensional (2D) myocardial deformation by speckle tracking***:** Myocardial tissue deformation (strain) was calculated during systole by speckle tracking echocardiography using Toshiba 2D Tissue Tracking system. All global deformation indices were calculated from cardiac cycles acquired and digitally stored on hard disc using an off-line analysis. Global longitudinal strains (GLS) as a reflection of longitudinal endocardial LV mechanics were measured from three conventional apical imaging planes at the end of systole; peak systolic strain was defined as the highest deformation at each plane and the average value was calculated [43]. Global radial strain (GRS) as an index of radial myocardial shortening was obtained from short axis view at the papillary muscle level [44].

Cardiac biomarkers

Plasma samples for determining N-terminal prohormone brain natriuretic peptide (NT-pro-BNP), high-sensitivity C-reactive protein (hs-CRP) and troponin T (TnT) were taken at the start and at the end of the study period. The samples were taken before the dialysis session, from the arterial blood line, one day after echocardiographic assessment. At the same day, the samples were analyzed in the local reference laboratory.

Troponin T was determined by a "sandwich" electrochemiluminescence immunoassay (ECLIA) method, on automatic analyzer (Cobas 501; Roche Diagnostics, Mannheim, Germany). The hs-CRP was measured using an immunoturbidimetric method (Cobas c501; Roche Diagnostics, Mannheim, Germany). The NT-proBNP was measured by a "sandwich" ECLIA method on the Cobas e 411 analyzer (Roche Diagnostic, Mannheim, Germany).

Biochemical parameters

Biochemical parameters were analyzed in the local laboratory from blood collected during the routine patient round before the second weekly session, at the start and at the end of the study including: hemoglobin, albumin, total iron-binding capacity (TIBC), urea, creatinine, intact parathyroid hormone (iPTH), calcium (Ca), phosphate (P), cholesterol (C), low-density lipoprotein-C (LDL-C), high-density lipoprotein-C (HDL-C) and triglycerides. A dialysis dose – the product of the urea clearance (K) over the urea distribution volume (V), and the dialysis session length (t), i.e. Kt/V was measured as single pool Kt/V according to the Daugirdas' formula [45]. During the study, all subjects continued to take their regular medications as indicated by referring doctors. Dialysis modality and dialysis prescription remained constant during the study unless referring doctor changed it based on his/her clinical judgment.

Data collection and statistical analysis

All patients were assigned identification codes to maintain confidentiality. Blood pressure data, HD prescription and all HD treatment data were abstracted from Dialysis charts and entered into an online database created for this study.

Statistical analysis was conducted using IBM SPSS Statistics 19.0 computer program (IBM, USA, 2011). All continuous variables were described in the form of the mean ± standard deviation (SD) except biomarkers which were given as median [interquartile range (IQR)] values. The categorical variables were expressed as percentages and examined using the χ^2 test; the Yates's correction for continuity was used for 2×2 contingency table. Relationship between variables was tested by Pearson's coefficient correlation. Intragroup comparisions of parametric continuous variables were performed by the paired *t*-test; for non-parametric variables the Wilcoxon signed rank test was used. In addition, the McNemar test was used to compare results of binary variables at baseline and at the end of the study. Comparisions of parametric variables between 2 groups were performed by independent *t*-test; non-parametric variables were tested with the Mann-Whitney *U* test. The normality distribution of data was tested by the Shapiro-Wilk test (subject number in the group less than 50). All the analyses were evaluated at the level of statistical significance of $p < 0.05$.

Results

Baseline characteristics

Patients in both groups were of similar age, predominantly male with high prevalence of hypertension (Table 1). The LVH assessed by basic echocardiography had 69 out of 83 patients (83.1%). Left ventricular hypertrophy and hypertension were not correlated with presence of residual renal function ($r = -0.043$; $p = 0.702$ and $r = 0.120$; $p = 0.279$, respectively).

Diastolic dysfunction was registered in 77 (92.1%) patients (Table 1). Arterial pressure in both groups was similar. Also, Av_ROH, Av_postROH and WG_Av were similar between the groups. The "critical" post-dialysis dehydration (Av_ROH < -6%) was correlated with Wg_Av > 5% ($r = 0.223$; $p = 0.049$) in the whole study group.

Of the 83 that enrolled, 73 patients completed the study, including 38 patients (24 males) in the active group and 35 patients (21 males) in the control group (Figure 1).

Patients in the active group exhibited a significant reduction in volume overload from baseline to the end of the study: 45% of active patients were found to have an Av_ROH > 15% at baseline while at the end of the study only 24% were above the 15% Av_ROH threshold.

Table 1

Baseline patients' characteristics

Parameters	Active group (n = 42)	Control group (n = 41)	*p* value
Age (years), mean ± SD	56.1 ± 11.5	57.5 ± 13.2	0.596
HD vintage (months), mean ± SD	79.9 ± 59.2	95.3 ± 80.0	0.600
Males, %	59.5	56.1	0.925
Arterial hypertension, %	76.2	70.7	0.573
Diabetes mellitus, %	11.9	7.3	0.737
Smokers, %	59.5	43.9	0.190
Diuresis ≥ 200 mL/24 h, %	28.6	34.1	0.756
HD session duration (hours, weekly), mean ± SD	12.5 ± 1.0	12.4 ± 1.1	0.814
Blood pump rate (mL/min), mean ± SD	277.2 ± 22.2	267.0 ± 25.6	0.422
Dialysate sodium (mmol/L), mean ± SD	142.1 ± 2.5	142.9 ± 2.7	0.178
HDF, %	33.3	19.5	0.214
Av_ROH (%), mean ± SD	11.8 ± 8.0	12.4 ± 7.0	0.702
Av_ROH > 15%, %	45.2	31.7	0.261
Av_postROH < - 6%, %	42.9	43.9	1.000
WG_Av (%), mean ± SD	4.5 ± 1.4	4.6 ± 1.7	0.751
LVH, %	81	85.4	0.770
DD, %	90.5	91.5	0.676
MAP pre HD (mmHg), mean ± SD	92.5 ± 10.0	88.4 ± 11.3	0.083
MAP post HD (mmHg), mean ± SD	84.6 ± 11.8	81.1 ± 10.7	0.158

HD – hemodialysis; HDF – hemodiafiltration; DD – diastolic dysfunction; Av_ROH – average weekly overhydration; Av_postROH – average weekly post dialysis overhydration; LVH – left ventricular myocardial hypertrophy; DD – diastolic dysfunction; AP pre HD – pre-hemodialysis mean arterial pressure; MAP post HD – post-hemodialysis mean arterial pressure; SD – standard deviation.

Table 2

Dialysis and hydration data in the study patients at enrollment time (0m) and after 9 months of study

Parameters	Active group (n = 38)			Control group (n = 35)		
	0 months	9 months	*p*-value	0 months	9 months	*p*-value
Av_ROH (%), mean ± SD	11.8 ± 8.3	10.3 ± 5.8	0.079	12.2 ± 7.2	11.3 ± 7.2	0.501
Av_ROH > 15%, n (%)	17 (44.7)	9 (23.7)	0.003	11 (31.4)	9 (25.7)	0.774
Av_postROH < - 6 %, n (%)	16 (42.1)	11 (28.9)	0.267	16 (45.7)	17 (48.6)	1.000
MAP pre HD (mmHg), mean ± SD	92.7 ± 10.4	91.2 ± 8.9	0.364	89.7 ± 10.7	91.3 ± 9.2	0.225
MAP post HD (mmHg), mean ± SD	84.6 ± 12.1	85.4 ± 18.0	0.655	81.9 ± 10.2	84.1 ± 12.0	0.235
HDF, n (%)	13 (34.2)	14 (36.8)	1.000	5 (14.3)	7 (20)	0.50
HD duration (hours, weekly), mean ± SD	12.5 ± 1.09	12.53 ± 1.14	0.922	12.43 ± 1.07	12.30 ± 1.02	0.413
Blood pump rate (mL/min), mean ± SD	272.6 ± 21.3	268.0 ± 27.5	0.217	268.1 ± 24.0	267.3 ± 20.6	0.806
Dialysate sodium (mmol/L), mean ± SD	142.1 ± 2.46	140.1 ± 1.7	< 0.001	142.9 ± 2.7	141.3 ± 2.7	0.001
Diuresis (≥ 200 mL), n (%)	10 (26.3)	10 (26.3)	1.000	13 (37.1%)	8 (22.9)	0.063

HD – hemodialysis; HDF – hemodiafiltration; MAP pre HD – pre-hemodialysis mean arterial pressure; MAP post HD – post-hemodialysis mean arterial pressure; Av_ROH – average weekly overhydration; Av_postROH – average weekly post dialysis overhydration.

The number of dehydrated patients increased in the control group, while it was slightly reduced in the cctive group. The residual renal function (RRF) declined only in the control group: 38% patients in this group with RRF function at the start of the study became anuric through the end of the study while there was no new anuric patients in the active group during the study. There was a rise in the pre-dialysis MAP from the beginning to the end of the study in the control group (1.63 mmHg higher after 9 months) while a decrease in MAP was observed in the active group (1.45 mmHg lower after 9 months), however the difference was not statistically significant in either group (Table 2). In both study arms, the dialysate sodium concentration was reduced at the end of the study and it was statistically significant ($p = 0.001$).

Biomarker and biochemistry data

At the end of the study, cardiac biomarkers did not change significantly either in the active or in the control group except for NT-proBNP concentration that significantly increased in control group ($p = 0.038$), (Table 3).

The biochemical parameters of the two groups of patients are shown in Table 4. In the active group a significant decrease was observed for serum albumin level and for TIBC. In the control group, patients had significantly improved hemoglobin, while TIBC, total C, HDL-C and serum P levels all worsened significantly (Table 4).

Table 3

Cardiac biomarkers in the study patients at enrollment (0 month) and after 9 months of study

Parameters	Active group (n = 38)			Control group (n = 35)		
	0 month	9 months	*p*-value	0 month	9 months	*p*-value
hs-CRP (mg/L)	4.02 (1.99–8.55)	4.42 (2.38–9.04)	0.577	3.86 (1.95–6.44)	4.09 (2.38–7.38)	0.169
TnT (μg/L)	0.048 (0.031–0.074)	0.048 (0.031–0.071)	0.689	0.052 (0.038–0.081)	0.052 (0.035–0.077)	0.224
NT-proBNP (pg/mL)	4527.0 (1449.3–10821.8)	4692.0 (1895.8–10033.8)	0.755	5810.0 (3339.0–15627.0)	8024.0 (4433.0–17467.0)	0.038

Biomarkers are given as median (interquartile range – IQR) concentrations.
hs-CRP – high sensitivity C-reactive protein; TnT – troponin T; NT-proBNP – N-terminal prohormone of brain natriuretic peptide.

Table 4

Main biochemical and nutritional parameters in the study patients at the time of enrollment (0 months) and at the end of the study period (9 months)

Parameters	Active group (n=38)			Control group (n=35)		
	0 months	9 months	*p*-value	0 months	9 months	*p*-value
Hb (g/dL), mean ± SD	10.5 ± 1.5	10.7 ± 1.4	0.609	9.9 ± 1.7	10.6 ± 1.7	0.032
Albumin (g/L), mean ± SD	40.3 ± 2.9	38.1 ± 4.0	< 0.001	39.2 ± 3.4	38.2 ± 2.9	0.092
TIBC (μmol/L), mean ± SD	41.5 ± 6.9	38.7 ± 7.1	0.007	40.3 ± 5.9	37.6 ± 8.8	0.012
Cholesterol (C) (mmol/L), mean ± SD	4.93 ± 1.10	5.07 ± 1.07	0.323	4.75 ± 0.73	4.32 ± 0.75	0.001
HDL-C (mmol/L), mean ± SD	1.08 ± 0.43	1.12 ± 0.50	0.509	1.07 ± 0.34	0.90 ± 0.28	< 0.001
spKt/V, mean ± SD	1.50 ± 0.32	1.54 ± 0.33	0.456	1.40 ± 0.26	1.40 ± 0.19	0.932
Ca (mmol/L), mean ± SD	2.31 ± 0.27	2.26 ± 0.24	0.083	2.34 ± 0.20	2.36 ± 0.22	0.837
P (mmol/L), mean ± SD	1.56 ± 0.52	1.47 ± 0.44	0.489	1.79 ± 0.54	1.60 ± 0.48	0.005
iPTH (pg/mL), median (range)	259.9 (100.8–588.1)	197.4 (97.5–482.9)	0.067	293.6 (106.0–582.8)	192.2 (78.0–625.2)	0.404

Hb – hemoglobin; TIBC – total iron binding capacity; HDL – high density lipoprotein; spKt/V – single pool Kt/V; P – phosphate; Ca – calcium; iPTH – intact parathyroid hormone.

Table 5

Doppler echocardiographic indices of cardiac structure and function in study arms at the enrollment (0 m) and after 9 months (9 m)

Parameters	Active group (n = 38)			Control group (n = 35)		
	0 months	9 months	*p*-value	0 months	9 months	*p*-value
LAV index (mL/m^2)	31.24 ± 11.61	29.57 ± 11.60	0.301	33.17 ± 12.39	35.37 ± 12.15	0.229
LVEDD (cm)	57.29 ± 6.03	55.97 ± 7.19	0.222	54.39 ± 6.31	55.72 ± 6.06	0.136
LVESD (cm)	41.39 ± 6.73	39.07 ± 6.85	0.024	37.23 ± 7.35	37.72 ± 6.73	0.669
LVEDV index (mL/m^2)	71.73 ± 23.83	65.55 ± 22.18	0.103	71.73 ± 23.82	65.55 ± 22.18	0.576
LVESV index (mL/m^2)	40.19 ± 12.50	35.79 ± 13.53	0.023	34.59 ± 11.53	36.7 ± 14.82	0.665
LVEF (%)	41.27 ± 9.26	43.95 ± 8.84	0.006	45.66 ± 8.74	44.32 ± 9.34	0.292
LVEF ≥ 50 (%)	8 (21.1%)	12 (31.6%)	0.125	11 (31.4%)	8 (22.9%)	0.508
RWT	0.384 ± 0.070	0.387 ± 0.071	0.800	0.401 ± 0.065	0.394 ± 0.047	0.476
LVM index (g/m^2)	147.09 ± 42.12	133.80 ± 33.57	0.003	135.68 ± 29.39	139.93 ± 35.72	0.372
LVMI index$^{2.7}$ (g/m$^{2.7}$)	62.81 ± 19.74	57.74 ± 16.87	0.007	60.35 ± 13.06	62.55 ± 16.97	0.301
FS (%)	27.86 ± 5.94	29.86 ± 5.83	0.056	30.71 ± 7.06	31.63 ± 5.52	0.466
E/e' med	12.52 ± 6.79	11.99 ± 3.75	0.690	12.68 ± 4.54	13.21 ± 4.10	0.342
E/e' lat	10.35 ± 4.73	9.96 ± 3.43	0.777	10.59 ± 5.00	11.12 ± 4.06	0.036
GLS LV Strain (%)	-9.56 ± 3.96	-10.37 ± 4.02	0.118	-10.18 ± 3.97	-10.28 ± 4.26	0.888
RS LV Strain (%)	18.56 ± 10.24	21.79 ± 12.16	0.014	24.21 ± 13.62	22.43 ± 12.07	0.550
Right Ventricle (mm)	35.10 ± 7.56	35.13 ± 7.35	0.983	35.38 ± 6.40	36.06 ± 7.37	0.598
TAPSE (%)	21.66 ± 5.29	21.61 ± 4.06	0.839	22.79 ± 5.72	21.02 ± 3.75	0.136
RVSP (mmHg)	35.69 ± 11.24	35.01 ± 9.30	0.565	34.84 ± 10.18	38.76 ± 8.34	0.028
IVCi (mm/m^2)	7.33 ± 2.58	7.36 ± 2.07	0.949	8.35 ± 2.79	8.97 ± 2.87	0.178
IVC-CI (%)	55.66 ± 24.56	56.20 ± 16.72	0.908	49.35 ± 15.33	49.07 ± 16.01	0.928

Results are given as mean ± standard deviation or number (%) of patients.
LAV index – left atrial volume index; LVEDD – left ventricle end-diastolic diameter; LVESD – left ventricle end-systolic diameter; LVED-VI – left ventricle end-diastolic volume index; LVESVI – left ventricle end-diastolic volume index; LVEF – left ventricle ejection fraction; RWT – relative wall thickness; LVMI – left ventricular mass index; LVMI$^{2.7}$- left ventricular mass indexed by height$^{2.7}$; FS- fractional shortening of the LV; GLS - Global longitudinal strain; GRS - global radial strain; TAPSE- tricuspid annular plane systolic excursion; IVC- inferior vena cava; IVCi- inferior vena cava index; IVC-CI- inferior vena cava collapsibility index; E/e' med - ratio of the peak trans-mitral filling velocity early in diastole (E wave) and the early relaxation LV velocity measured on medial (septal) part of the mitral annulus (e'med); E/e' lat- E/e' ratio where e' is measured on lateral part of the mitral annulus; RVSP - right ventricle systolic pressure

Hemodynamic data

The average LVEF was improved after 9 months in the active group [from 41.27 to 43.95%, ($p = 0.006$)] and this difference was not observed in the control group (Table 5). In addition, patients from the active group significantly improved their LVESD ($p = 0,024$), LVESVI ($p = 0.023$), LVMI ($p = 0.003$), $LVMI^{2.7}$ ($p = 0.007$) and GRS LV strain ($p = 0.014$). In the control group, patients significantly increased E/e' lat and RVSP, indicating worsening of diastole LV function. Other parameters remained unchanged (Table 5).

The main structural changes in the active group of patients were a reduction of LVMI as well as $LVMI^{2.7}$, while main functional improvements after 9 months of AFM was better LVEF and FS in accordance to improvement of radial LV mechanics detected by higher GRS.

Discussion

This study confirmed that our HD patients had very high prevalence of LVH and diastolic dysfunction (83% and 92%, respectively) along with high average weekly OH. During the study, patients in the active group significantly improved their overhydration but also several cardiac parameters including MAP, LVEF, LVESD, LVESV index, LVM index, LVM $index^{2.7}$, and GRS LV strain. On the other hand, patients in the control group, managed by routine clinical assessment, exhibited a deterioration of diastolic function and, consecutively, RVSP. These functional changes were associated with significantly higher levels of NT-proBNP in this group of patients. These findings were associated with better Av_ROH management in the active group, and the percent of "critically" overhydrated patients decreased from 45% to 24% from baseline to the end of the study period. The reduction of critically overhydrated patients by BIS guided fluid management is consistent with the findings of others [19, 29, 46].

There are numerous studies concerning the degree of hydration and cardiovascular impairment in end stage kidney disease (ESKD) patients [8, 9, 27, 29–31], as well as about the association of chronic fluid overload assessed by BIS with LVM and level of cardiac biomarkers [28]. However, to the best of our knowledge, there is no prospective study addressing the influence of DW probing either by BIS or by other methods to LV performance, especially LVM with myocardial mechanics and cardiomarkers. There are few prospective randomized studies that used BIS measurements to target post-dialysis weight which showed significant improvement in LVM and/or blood pressure regulation although the BIS measurements were performed twice monthly [30] or even less frequently [31]. A study by Moissl et al. [29] addressed the issue of using one standard protocol for the implementation of BIS measurements in clinical practice for patients on chronic HD program. That study was not randomized, lasted 3 months, and echocardiography was not performed.

Patients from whole study group had global myocardial strains values below the normal range. Lower contractility was reflected by lower LVEF at the beginning of the study (74% of patients had LVEF under 50%). Therefore, it is not surprising that strains, as indicators of LV contractility [47, 48] are far below the normal. The normal level of GLS in the general population is < -18% [44], but Krishnasamy et al. [38] suggested a level of GLS < -16% as normal for HD patients population. If we had used this criteria for GLS, there would have been just 6 of 73 patients at the start and only 3 at the end of the study with normal values in both groups. Although GLS, in general, did not improve much during the study in the active group, radial contractility, expressed by GRS, significantly enhanced, suggesting that optimal changes in volume load influenced primarily radial myocardial shortening with pump function upgrading.

Patients in the control group had deteriorated diastolic function as assessed by E/e' raise and also of RVSP, and this was followed by an increase of NT-proBNP. Moissl et al. [29] did not observe any improvement in BNP level in their study after 3 months and based only on volemia criteria. However, there was no data regarding LVM, or degree of diastolic dysfunction in observed population. In addition to volemic status, one could speculate that NT-proBNP correlates with diastolic dysfunction as well [49].

It is important to mention that apart from overhydration before HD, there was a high proportion of post-dialysis dehydrated patients (i.e. with Av_postROH< -6%) in both groups (over 43%) at the start of the study. According to our results, almost every second patient in the control group (49% of them) was dehydrated after dialysis more than 6% of their ECW at the end of the study. In other studies, the proportion of such underhydrated patients was smaller – in a range from about 3% to 30% [19, 26, 29, 46, 50]. One possible explanation is that most of the patients in this study had a long dialysis experience and wished to avoid overt overload syndrome, so they refused increases in their dry weight. Also, post-dialysis dehydration closely correlated with higher weight gain (i.e. "overhydration" in terms of clinically targeted DW) indicating a limitation of a thrice weekly dialysis schedule. The consequences of post-dialysis dehydration are not clearly described in the literature but it may influence patients' quality of life and expose them to a risk of hypotension and its consequences. Still, our dehydrated patients in both study groups did not change their MAP significantly which cannot be explained by our study protocol. Therefore, our experience indicates that DW needs to be established with care. This process is time-dependent and requires a full compliance from the patient before achieving the goal.

When establishing the appropriate dry weight for an individual patient, the influence on residual renal function must be taken into account. According to our experience, patients in the active group maintained their residual diuresis during the study period. However, there was a significant decrease in the proportion of the patients with residual diuresis in the control group. Our results demonstrated a significant reduction in dialysate sodium among patients in both study arms. As was mentioned previously, daily visits by physicians include the monitoring of DW and dialysis parameters including dialysate sodium. Therefore, it was not surprise that the control group had fewer extremely overhydrated patients at

the end of the study as compared with the study start. These cofactors may influence the overall results of the study.

Finally, deterioration of some nutritional parameters (serum albumin and TIBC) could be explained by stricter dietary control during the study. The values of serum albumin and TIBC remained in the reference range but did not suggest any malnutrition.

Limitations of the study

It was single center study that included a relatively small sample of the participants. Cardiac structure, function and mechanics was performed only by 2D echocardiography without other imaging techniques.

Conclusion

Bioimpedance spectroscopy measurements implemented through the active fluid management concept had positive impact on cardiac hemodynamics and mechanics in our study patients. Comprehensive evaluation of cardiac structure/function and cardiac biomarkers shed more light in determining dry weight in dialysis patients.

Active fluid management in everyday clinical practice could improve clinical decisions regarding optimal weight and further clinical course in hemodialysis patients. Well designed studies are needed urgently to investigate the value of guided fluid management approaches.

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Disclosures

MDM, NMN, NR and NR declare no conflict of interest with the content of this manuscript. ZP is the employee of the Special Hospital for Hemodialysis "Fresenius Medical Care" Belgrade. "Fresenius Medical Care" is the manufacturer of the BCM device and was not involved in the design or conduct of the study.

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