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PROCENA STATUSA VOLEMIJE ULTRAZVUČNIM PREGLEDOM DONJE ŠUPLJE VENE I SPEKTROSKOPSkom BIOIMPENDANCOM KOD BOLESNIKA NA HEMODIJALIZI

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Abstract

Background/Aim. Hypervolemia is an important risk factor for the development of cardiovascular morbidity and mortality in patients treated with regular hemodialysis. There is still no reliable method for assessing the status of volemia in these patients. The aim of the study was to assess the status of volemia in patients treated with regular hemodialysis by measuring the parameters of the inferior vena cava and bioimpedance. Methods. Authors examined the effect of hemodialysis treatment on ultrasound parameters of the inferior vena cava, as well as on the parameters measured by bioimpedance before and after hemodialysis. The N-terminal prohormone of brain natriuretic peptide (NT-proBNP) values were measured both before and after hemodialysis. Patients (45) were involved in the non-interventional cross-section study, who were treated with standard bicarbonate dialysis. According to the intradialytic yield, the patients were divided into three groups: I (up to 2000 ml), II (2000–3000 ml), III (over 3000 ml). Results. The values of the inferior vena cava parameters and the parameters measured with bioimpedance are significantly lower after treatment with hemodialysis (p<0.005). The third group of patients had a significantly higher total fluid volume in the body, compared to group I, as well as significantly greater volume of extracellular fluid (p<0.005). Significantly lower values of NT-proBNP in all groups (p<0.005) were detected after hemodialysis. After treatment with hemodialysis, a positive correlation was observed between the concentration of NT-proBNP in the serum and the extracellular/intracellular water ratio, however, the correlation between NT-proBNP concentration and total fluid measured by bioimpedance spectroscopy did not reach statistical significance. Conclusion. Measurement of the inferior vena cava ultrasound parameters and volemia parameters using bioimpedance significantly contributes to the assessment of the status of volemia, but it can’t be used as a separate parameter, but in combination with all other methods.

Key words: volemia; ultrasound examination; inferior vena cava; spectroscopic bioimpedance; hemodialysis.

Apstrakt

Uvod/Cilj. Hipervolevija je značajan faktor rizika za razvoj kardiovaskularnog morbiditeta i moratliteta kod bolesnika koji se leče redovnom hemodijalizom. Još uvek ne postoji suverena metoda za procenu statusa volemije kod ovih bolesnika. Istraživanje je imalo za...
cilj da proceni status volemije kod bolesnika koji se leče redovnom hemodijalizom merenjem parametara donje šuplje vene i bioimpendancmetrijom. **Metode.** Ispitivan je uticaj tretmana hemodijalizom na ultrazvučne parametre donje šuplje vene, kao i na parametre merene bioimpedantnom spektrometrijom (BIS) pre i posle hemodijalize. Merene su i vrednosti N-terminalnog prohormona moždanog natriuretskog peptida (NT-proBNP) pre i posle hemodijalize. U neinterventnu studiju preseka bilo je uključeno 45 bolesnika koji se leče standardnom bikarbonatnom dijalizom. Prema intradijaliznim prinosom bolesnici su podeljeni u tri grupe: I (do 2000 ml), II (2000-3000 ml), III (preko 3000 ml). **Rezultati.** Vrednosti parametara donje šuplje vene i parametara izmerenih BIS-om su značajno niži nakon tretmana hemodijalizom (p<0,005). Treća grupa bolesnika imala je značajno veću ukupnu zapreminu tečnosti u organizmu pre hemodijalize u poredenju sa I grupom, kao i značajno veću zapreminu vančelijske tečnosti (p<0,005). Nakon hemodijalize detektovane su značajno niže vrednosti NT-proBNP-a u svim grupama (p<0,005). Posle tretmana hemodijalizom, zabeležene je pozitivna korelacija između koncentracije NT-proBNP-a u serumu i odnosa ekstracelularne/intracelularne tečnosti, medjutim korelacija izmedju koncentracije NT-proBNP-a i ukupne tečnosti izmerene bioimpedantnom spektroskopijom nije dostigla statističku značajnost. **Zaključak.** Merenjem ultrazvučnih parametara donje šuplje vene i parametara volemije BIS-om bioimpendacmetrijom u značajnoj meri doprinose proceni statusa volemije, ali se ne mogu koristiti kao odvojeni parametar, već u kombinaciji sa svim drugim metodama.

**Ključne reči:** volemija; ultrazvučni pregled; donja šuplja vena; bioimpedantna spektroskopija; hemodijaliza.

**Introduction**

Hypervolemia is an important risk factor for the development of cardiovascular morbidity and mortality, as well as adverse outcome in patients treated with regular hemodialysis. The assessment of volemia status in these patients is performed by clinical examination, lung radiography, ultrasound examination of the lungs, ultrasound examination of the inferior vena cava, ultrasound of the heart, measurement of volemia using bioimpedance spectroscopy (BIS), and by monitoring of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the serum.
The goals of hemodialysis are to eliminate excess fluid, achieve adequate dry weight and depuration of the organism from uremic toxins and regulation of electrolyte imbalance. Dry weight is the weight obtained at the end of a regular dialysis session, below which the patients will most likely develop symptomatic hypotension.

Symptomatic hypotension is associated with the rate of ultrafiltration during hemodialysis treatment and the rate at which the removal is performed. Inadequate dry weight assessment leads to chronic volume overload. Removing too much excess fluid (below the dry weight) causes hypovolemia and vertigo, headache, pain and cramps in the muscles, and a decrease in perfusion of vital organs occurs. In cases where the elimination of fluid is not sufficient (weight above the dry weight), a chronic hypervolemic condition and complications occur, such as: hypertension, left ventricular hypertrophy, diastolic dysfunction, congestive heart failure and oedema of the lungs.

Radiography of the heart and lungs is highly specific but with low sensitivity for the conditions of hypervolemia. Disadvantage of this diagnostic method is that it sometimes takes several hours for the radiographic changes of hypervolemia to occur. In addition, in 20 to 40% of patients, radiographic changes of hypervolemia are absent. What is important when assessing the status of volemia is echocardiographic examination of the heart to assess the structure and function of the left ventricle, as well as the disorder of left ventricular systolic and diastolic function. This examination may indicate the condition of hypervolemia, but it does not give us information that the patient is in normovolemia.

Ultrasound of the lungs is used to estimate the volume of fluid in the extravascular lung section and the severity of the degree of hypervolemia. This method is useful in detecting pulmonary congestion even before the manifested clinical picture, and it correlates well with systolic cardiac function. The disadvantage of this method is that it may not always correlate with hypervolemia.

The results of numerous studies indicate that hyper- or hypovolemia can be determined in a dialysis patient using ultrasound measurement of the diameter of the inferior vena cava (IVC). However, the recommended values of the IVC diameter (IVCd) that would correlate with optimal body weight are not generally accepted because of individual variations, as well as due to significant subjectivity in the measurement. In their study, Jose Muniz Pazeli, et al concluded that ultrasound of the IVC could be performed by nephrologists who have little experience in ultrasound and the findings were
potentially useful for dry weight assessment in patients on dialysis. The IVCd, IVC index (IVCi), and IVC collapsibility index (IVCci) are measured using ultrasound examination of IVC. The normal diameter of the IVC is 15-20 mm, and it varies depending on the breathing cycle. In the inspirium, the diameter decreases and amounts to 0-15 mm, and in the expirium it increases and amounts to 15-20 mm. The anterior-posterior diameter of the IVC was measured subxiphoidally, at a distance of 2-3 cm from the right atrium during spontaneous breathing, forced inspiration and forced expiration (Figure 1). The IVCi is the ratio of the IVCd and the body surface (BS) of the patient IVCd/BS (mm/m^2). The normal IVCi is 8.0-11.5 mm/m^2 (euvolemia). The IVCi below 8 mm/m^2 indicates hypovolemia, and over 11.5 mm/m^2 is considered as hypervolemia. In order to calculate the IVCci, it is necessary to measure its diameter in inspirium (IVC insp) and expirium (IVC exp). The IVCci is calculated using the formula: IVCci = [(IVC exp - IVC insp)/ IVC exp] × 100%. If the IVCci is 50 to 75%, we are talking about euvoelema, if it is below 50% about hypovolemia, and over 75% about hypervolemia.

Additionally, in assessing the status of volemia in hemodialysis patients was used to concentration of NT-proBNP in plasma, which has a significant prognostic value for cardiovascular mortality in these patients. NT-proBNP is often increased in patients with chronic renal failure. When examining patients with asymptomatic chronic renal failure who have not yet started dialysis treatments, an increased level of NT-proBNP was observed in more than half of the patients. However, there is no clear cut-off in the literature for the concentration of NT-proBNP that would distinguish cardiac from renal failure (cut-off values range from 5000 to 7000 pg/ml). NT-proBNP is not only specific for hypervolemia but also for nutritional status, systolic and diastolic left ventricular dysfunction.

Precise assessment of the status of volemia in patients on dialysis also includes the analysis of bioimpedance spectroscopy. Bioimpedance represents the total resistance of tissue and fluid to the flow of micro-amperage alternating current through the body. There are two methods that work on the principle of bioimpedance spectroscopy (BIS). One is the so-called “whole body BIS”, where the electrodes are placed on the wrist and ankle on the same side of the body, and using appropriate mathematical and physiological tissue models, we obtain data on the total amount of water in the body (TBW) and on the amount of water in tissue cells. The second method of bioimpedance spectroscopy is a
segmental BIS, which separately measures the amount of water in the extremities and the trunk. It can be done with eight electrodes, it is very precise, but the examination lasts for longer time and in practice it has not shown an advantage in relation to the whole body BIS 21, 22.

A shift in the application of bioimpedance spectroscopy to determine the condition of volemia in hemodialysis patients was provided by two studies published in 2009. These studies have shown that: 1) hypervolemia prior to dialysis treatment greater than 15% of normal extracellular fluid (approximately 2.5 L in an average person of 70 kg) correlated with a twice higher risk of fatal outcome during the 3.5 year follow-up period, compared to those patients in whom this pre-dialysis hypervolemia was lower 23; 2) Reduction of this “critical” hypervolemia can improve arterial blood pressure values and reduce therapy in hemodialysis patients 24.

The aim of this study was to investigate the degree of association between the status of volemia assessed clinically (interdialysis yield), with IVC measurement, BIS, and determination of NT-proBNP, and the values of the parameters measured by BIS. Also, we determined the influence of hemodialysis treatment on the concentration of NT-proBNP in the serum of the patients. In further research, we also examined the influence of the degree of ultrafiltration on the values of the parameters of ultrasound examination of the inferior vena cava, as well as the degree of correlation between NT-proBNP in the serum and the parameters of ultrasound examination of the inferior vena cava before and after hemodialysis.

Methods
Patients: A cross-sectional study (non-interventional study) included 45 patients treated with regular hemodialysis for more than three months. According to the rate of targeted ultrafiltration, the patients were divided into three groups. The first group consisted of patients with the yield of up to 2000 ml (n=14), the second group consisted of patients with the yield of 2000 ml to 3000 ml (n=12) and the third group of patients with the yield of over 3000 ml (n=19). Patients were dialysed using low-flux and high-flux synthetic dialysers, 12 hours a week, using a bicarbonate ultrapure hemodialysis solution, and the machines type Fresenius 4008, 508S and Gambro AKA20US and Gambro Artis. The study
was conducted at Center for Nephrology and Dialysis of Clinical Centre of Kragujevac, with respect to the Helsinki Declaration and good clinical practice.

**Biochemical analyses:** The following examination parameters were determined in all the patients: CBC, status of iron in the organism (serum iron concentration, transferrin saturation, serum ferritin concentration), parameters of secondary hyperparathyroidism (serum calcium concentration, serum phosphate concentration, solubility product (calcium concentration, serum phosphate concentration), serum alkaline phosphatase concentration, serum intact parathyroid hormone concentration), micro-inflammatory parameters (C-reactive protein), nutritional status parameters (concentration of total protein and serum albumin). The concentrations of NT-proBNP in the serum were assessed 15 minutes before the start of hemodialysis and 15 minutes after the shutdown of hemodialysis. The adequacy of hemodialysis was assessed on the basis of Kt/V index (dialysis dose, i.e. product of urea clearance during dialysis (K) and time of dialysis procedure (t) divided by urea distribution volume, V) and URR index (Urea Reduction Ratio). Laboratory parameters were sampled in accordance with a laboratory test protocol for patients who were treated in the chronic hemodialysis program, there was no need for additional blood sampling.

**BIS was performed by Body Composition Monitor modul (BCM; manufacturer Fresenius Medical Care, Software version: 3.2):** the patient's hydration status was assessed 15 minutes before the start of hemodialysis and 15 minutes after the shutdown of hemodialysis. The electrodes were placed on the wrist of one hand and the foot on the same side of the body, of the patient who is in a lying position. This BIS device uses a multi frequency current range (50 different frequencies from 5 to 1000 KHz) and obtained data on the total body water (TBW), the extracellular fluid (ECF), the intracellular fluid (ICF) and the quantification of the excess volume of ECF. The results are displayed on the monitor after 2 minutes of measurement and are stored on a card for each patient individually.

**Ultrasound examination of the IVC:** The examination was performed on LOGIQ P5 ultrasound apparatus by using a 3.5 MHz probe. The anterior-posterior diameter of the IVC (IVCd) was measured in its proximal during spontaneous breathing and during inspiration (IVC insp) and expiration (IVC exp), 30 minutes before and after the shutdown of hemodialysis, subxyphoidally at a distance of 2-3 cm from the right atrium of the heart. Based on the measured IVC parameters, the IVCi and IVCci were determined.
**Statistical Data Processing:** The data were processed in the statistical software SPSS 20.0 for Windows (IBM SPSS Statistic for Windows, Version 20.0, USA). The results are presented as SEM±SD for numerical and as frequency for attribute data. The following was used for statistical analysis of the obtained data: The Kolmogorov-Smirnov test (estimation of the normality and distribution of data), the Student's t-test, the Mann-Whitney U test, the single-factor analysis of variance – ANOVA, the Kruskal-Wallis test, the univariate and multivariate logistic regression analysis, the Spearman and Pearson's correlation coefficient. The significance threshold was 0.05.

**Results**

**Table 1.** Shows general patient data that include analysis of demographic and clinical characteristics. The values of the measured biochemical parameters are also shown.

**Graph 1.** Shows the percentage representation of patients according to the rate of ultrafiltration.

**Influence of the rate of ultrafiltration on the examined parameters used to assess volemia**

By comparing the mean values of ECF between the three groups, it was found that they were not equal. Namely, the third group (ultrafiltration greater than 3000 ml) had significantly higher ECF values than the first group (p=0.017) and compared to the second group (p=0.025). Statistically significant difference in comparison of TBW was recorded only between the first and the third group of patients (p=0.046) in **Table 2.**

**Mean values of extracellular fluid in examined patient groups**

Statistically significant differences were not detected between the groups when the values of NT-proBNP, IVCd, IVCi, IVC insp, IVC exp, IVCici and the ECF/ICF ratio were compared. The mean values of ECF are shown in **Graph 2.**

**Comparison of the examined parameters before and after hemodialysis**

The values of laboratory findings, ultrasound (IVCd, IVCi, IVCici) and volemia parameters used to assess the clinical condition of patients were statistically significantly lower after hemodialysis, except in the measurement of IVC values (p=0.990). The values of IVCici 30 minutes after hemodialysis were statistically significantly higher compared to the values of this parameter before hemodialysis (48.15±11.38 vs. 55.45±15.07; p=0.008). This result suggests that the patients switched from the state of hypervolemia to the state of euvolemia...
after hemodialysis. This was corroborated by the result of weight changes before and after hemodialysis. The results of these comparisons are given in Table 3.

The degree of correlation of serum NT-proBNP values with other before-hemodialysis parameters

Positive correlation was detected of serum NT-proBNP with ultrasound parameters VCI d, VCI i, VCI ins, VCI exp, VCI ci and changes in body weight. NT-proBNP is also positively correlated with the ECF/ICF index and weight change. Persons with higher values of NT-proBNP lose more body fluid. NT-proBNP is in a negative correlation with the VCI collapsibility index, which means that higher NT-proBNP values are in correlation with lower VCI collapsibility index. That is, the patients in hypervolemia have high NT-proBNP and low VCI collapsibility index in Table 4.

The degree of correlation of serum NT-proBNP values with other parameters after hemodialysis

Correlations of NT-proBNP with ultrasound parameters and volemia condition parameters after dialysis are shown in Table 5.

It can be seen that after hemodialysis, NT-proBNP is positively correlated with volemia, body weight, and ECF/ICF index. However, a negative correlation was recorded between NT-proBNP and IVCci, which was on the border of statistical significance (p=0.060).

Discussion

The results of many studies suggest that hyper- or hypovolemia in patients on hemodialysis can be determined by ultrasound measurement of the diameter of the inferior vena cava (IVC d) \(^{26, 27}\). In terms of the significance of the IVCd and the correlation of this parameter with hypervolemia, the results of previous studies are contradictory. Sonmez, et al \(^{28}\), based on the results of their study, recommend that the values of normal hydration be defined as IVCd values greater then ≥11.6 mm/m\(^2\) in the expirium or above 9.8 mm/m\(^2\) in the inspirium. Contrary to these results, it is usually stated in the literature that the IVCd indexed to body surface (IVCi) greater than 11.5 mm/m\(^2\) correlates with mean pressure in the right atrium greater than 7 mmHg, or with significant hypervolemia, while this index smaller than 8 mm/m\(^2\) correlates with significant circulatory hypovolemia. However, this index is not sufficiently accurate, as other factors such as: heart rate, arterial pressure and antihypertensive drug therapy have an effect on it.
The results of our study show that there was no statistically significant difference in the measurement of the IVCd during normal breathing, inspirium and expirium, between the three groups of patients with different degrees of ultrafiltration. A statistically significant difference was observed by comparing the IVCd before and 30 minutes after hemodialysis. After hemodialysis, the IVCd significantly decreases.

In the available literature, it is stated that the values of NT-proBNP positively correlate with the risk of mortality in patients on dialysis. However, one measurement of the NT-proBNP value can’t be a reliable parameter of the assessment of the condition of volemia, because it depends on both the volemia and the degree of myocardial damage. However, serial measurement of this marker may be a good indicator of the condition of volemia measured by bioimpedance. In our study we measured the values of NT-proBNP before and after hemodialysis. Our results show that the measured values of NT-proBNP before hemodialysis positively correlate with the inferior vena cava diameter. Also, the higher NT-pBNP values before hemodialysis were positively correlated with ECF/ICF and body fluid changes. However, only positive correlation between the value of this marker and the condition of volemia was recorded by measuring the value of NT-pBNP after hemodialysis. The results of our study are similar to the results of a study in which the cut-off for the value of NT-proBNP was determined (from 5000 to 7700 pg/ml) as an indicator of hypervolemia. In their cross section study, Velasco, et al described an excellent correlation between the average volemia assessed by BCM before hemodialysis and the levels of NT-pBNP measured before hemodialysis in patients aged up to 72 years. In the study by Paunic et al. normovolemic patients (also estimated by BIS measurement) has NT-proBNP up to 4700 pg/ml and hypervolemic has this value above 5800 pg/ml.

A recent study by David, et al showed a significant correlation between serum NT-proBNP and the ratio of extracellular water and body weight only in hemodialysis patients with systolic left ventricular dysfunction, but not in those without systolic dysfunction. Although the level of NT-proBNP can be increased with the increase in volume load, the summary of currently available evidence gives the impression that this marker has a limited role in assessing the state of hydration in the dialysis population. The use of this cardiac biomarker in assessing the condition of volemia in patients on hemodialysis has not yet entered the standard procedure due to the high cost and poor specificity of the tests, as well as due to the lack of a clear criterion for the normal range of NT-pBNP values in
hemodialysis patients. Consistent with the above study results, the results of our study cannot provide a clear cut-off value of NT-proBNP (range 5188 to 7536 pg/ml).

Our results show that hemodialysis treatment has a statistically significant effect on the values of parameters for assessing the state of volemia measured by BIS. The values of the parameters measured by BIS after hemodialysis treatment are highly statistically significantly lower compared to the values before hemodialysis. Our results correlate with the results of the study they conducted by Chamney, et al.

Also, our results show that the parameters obtained by BIS provide objective, qualitative and useful data on the state of volemia in patients treated with hemodialysis. The results obtained by this method correlate with the biohumoral cardiac marker NT-proBNP. Similar results were obtained in the study by Velasco, et al.

Conclusion
Neither the inferior vena cava diameter nor bioimpedance spectroscopy nor NT/proBNP measurement can’t be used as a stand alone test for monitoring the condition of hydration of patients on hemodialysis. The results obtained by these methods must be interpreted individually and adapted for each patient. Only in this way, these parameters could add the value to the clinical judgment of an individual hemodialysis patient optimal body weight.

Conflict of interest: None declared.

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