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KADRIYE ÖZDEMİR

MAKBULE SEVGİ MİR

NİDA DİNÇEL

SİBEL BOZABALI

İPEK KAPLAN BULUT

See next page for additional authors

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Authors

KADRIYE ÖZDEMİR, MAKBULE SEVGİ MİR, NİDA DİNÇEL, SİBEL BOZABALI, İPEK KAPLAN BULUT, EBRU YILMAZ, and BETÜL SÖZERİ

Bioimpedance for assessing volume status in children with nephrotic syndrome

Kadriye ÖZDEMİR^{1*}, Makbule Sevgi MİR¹, Nida DİNÇEL¹,
Sibel BOZABALI², İpek KAPLAN BULUT¹, Ebru YILMAZ¹, Betül SÖZERİ¹

¹Department of Pediatric Nephrology, Faculty of Medicine, Ege University, İzmir, Turkey

²Department of Pediatric Cardiology, Faculty of Medicine, Ege University, İzmir, Turkey

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Background/aim: The effectiveness of assessing volume load via bioimpedance in pediatric patients with nephrotic syndrome (NS) was investigated.

Materials and methods: Patients with NS (n = 34) were compared with healthy controls (n = 20). The inferior vena cava index and inferior vena cava collapsibility index (IVCCI) scores were determined for all subjects. Bioimpedance measurements were used to directly determine volume load. Clinical findings, relative fluid load, and echocardiographic measurements were determined and compared with bioimpedance in calculating volume load.

Results: The sensitivity and specificity of bioimpedance in determining volume load were found to be 65% and 90%, respectively. IVCCI was lower in NS patients than in controls. There were also significant differences in IVCCI values between patients with localized and generalized edema. Relative fluid load was higher in NS patients with generalized edema as opposed to patients with localized edema. For calculating volume load, the sensitivity of bioimpedance, clinical findings, and echocardiographic measurements was 87%, 95%, and 83%, respectively, whereas the specificity of determining volume load by bioimpedance, clinical findings, and echocardiographic measurements was 50%, 10%, and 80%, respectively.

Conclusion: Our data suggest that bioimpedance may be superior to echocardiography in determining volume load in children with NS, because it is cost-effective, reliable, and relatively simple to perform.

Key words: Nephrotic syndrome, children, volume status, bioimpedance

1. Introduction

Edema is one of the most common symptoms in nephrotic syndrome (NS), and its pathogenesis is not completely understood. The current theory is that vascular underfill contributes to the development of edema (1,2). However, plasma volume and renin-aldosterone levels are normal in certain patients, which supports the idea that the mechanism of edema may be attributed to other causes (3,4). According to the overfill theory, edema results from increased salt retention due to a primary renal tubular defect. In fact, this is the prevailing theory in most recent studies of adult NS (5). Various methods have been created to assess volume load so as to discern how edema develops in patients with NS. In addition to clinical assessments, vasoactive hormones, echocardiography, and bioimpedance analysis have been frequently utilized in recent studies of edema in NS patients. However, such studies have not been performed to further elucidate the pathogenesis of edema in children with NS (6,7).

It can be difficult to measure biological markers such as atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) to assess volume status in patients with heart conditions, because obtaining these markers is costly and sometimes requires invasive procedures, and not every medical center is equipped to collect these in their laboratories. As such, the usage of these biomarkers is restricted, but echocardiography and the inferior vena cava collapsibility index (IVCCI) and inferior vena cava index (IVCI) are commonly used to determine intravascular volume, especially for hemodialysis patients (8–10). It is difficult to perform these techniques with pediatric patients as these measures often vary depending on the individual performing the test, and sometimes these tests do not accurately indicate the severity of the volume loss, which greatly reduces the utility of these methods (11,12).

Another technique used to determine volume status is body composition monitoring (BCM) with bioimpedance spectroscopy (BIS). This method has been recently utilized

* Correspondence: kcanturk1@hotmail.com

to determine patient fluid status, particularly for patients that are receiving hemodialysis. It performs measurements at 50 different frequencies ranging from 5 to 1000 kHz, and together with spectroscopy, this technique determines the electrical resistance of fluids in the body. BIS can determine the presence of excess bodily fluid so as to identify patients with hypervolemia. Moreover, total body fluid, extracellular fluid (ECF), intracellular fluid (ICF), lean tissue mass, and adipose tissue mass can be measured, too. Measuring total body fluid with BIS is often preferred as it has good precision and is noninvasive (13,14). The purpose of our study was two-fold: first, to investigate the effectiveness of BIS in determining volume load in pediatric NS patients with edema, and second, to compare conventional markers of volume status such as clinical findings, blood pressure, heart rate, and echocardiography with BIS.

2. Materials and methods

A total of 34 pediatric patients diagnosed with NS between 2010 and 2013 at the Department of Pediatric Nephrology at the Ege University School of Medicine were included in the study. From these 34 patients, 11 subjects were female and 23 were male. The Ethics Committee of the Medical Faculty of Ege University reviewed and approved this study. Patients with relapses or newly diagnosed NS who had not received steroid treatments within 6 months of study participation were included in the study. The control group comprised 20 healthy age-matched and sex-matched children. All testing and clinical assessments were performed by the same physician. Patients were diagnosed with NS via clinical and laboratory findings including edema, significant proteinuria ($\geq 40 \text{ mg m}^{-2} \text{ h}^{-1}$), hyperlipidemia, and hypoalbuminemia ($\leq 2.5 \text{ g/dL}$). Weight, height, weight according to height, body mass index, and blood pressure were determined for all study subjects. The presence of periorbital and pretibial edema along with acidosis was considered generalized edema. Cardiothoracic index (CTI) was calculated using the following equation from posterior-anterior chest X-rays taken at a distance of 180 cm from the patient while supine or standing:

$$\text{CTI} = \frac{\text{cardiac diameter}}{\text{thoracic diameter}}$$

CTI values that were at least 0.50 were considered within normal limits (15).

The presence of weight gain, edema, phase 1 or phase 2 hypertension, jugular vein distension, dyspnea and/or tachypnea, and hepatomegaly were clinical indicators of volume status. The IVCI and the IVCCI were measured by the same pediatric cardiologist that performed the

echocardiography. Patients performed deep inspirations and expirations while supine and after 5 min of resting so as to measure the diameter of the inferior vena cava while inspiring and expiring. The inferior vena cava diameter was measured 2 cm distal to the right atrium along the subcostal long axis. The 3S probe of the vivid 7-echocardiography device (GE Healthcare, UK) was used in 2D mode and M mode in order to measure the inferior vena cava diameter. The following formula was utilized to determine the IVCI:

$$\text{IVCI} = \frac{\text{expiration max. diameter (cm)} + \text{inspiration min. diameter (cm)}}{2m^2}$$

To determine the IVCCI, this equation was utilized:

$$\text{IVCCI} = \frac{\text{expiration max. diameter (cm)} + \text{inspiration min. diameter (cm)}}{\text{expiration max. diameter} \times 100}$$

In comparison with the control group, patients with NS demonstrating high IVCI and low IVCCI values were considered to have volume overload. General echocardiographic evaluations were performed to identify the presence of any preexisting cardiac pathology.

BIS measurements were utilized to determine whether volume overload was present. BCM (BCM, Fresenius Medical Care D GmbH, Germany) was measured using 4 special electrodes that were placed on the lower and upper extremities. Sex, height (cm), body weight (kg), and systolic and diastolic blood pressures (mmHg) were collected and recorded for every subject. Overhydration (OH), ECF, ICF, and relative fluid load, which is a percentage calculated by determining the ratio of OH to ECF, were noninvasively obtained via BIS. If the relative fluid load was found to be $\geq 15\%$, the patient was considered to be hypervolemic, and if the relative fluid load was determined to be $\leq 15\%$, the patient was considered to be normovolemic (16).

Descriptive statistics are presented as percentages, means, and standard deviations. Univariate analyses for group comparisons of continuous variables were performed using the Student t-test. Variables that did not follow a normal distribution were compared using the Mann-Whitney U test. A Pearson correlation analysis was performed for variables that followed a normal distribution, and a Spearman correlation analysis was used for variables that did not conform to a Gaussian curve. An analysis of variance test was used for multiple comparisons between groups. P-values of less than 0.05 were considered significant.

3. Results

The average patient age was 7.57 ± 2.25 years and all patients received no steroid treatment within 6 months prior to study participation. The patients were either

experiencing a relapse of NS (n = 26) or were newly diagnosed with NS (n = 8). A total of 20 age-matched and sex-matched children formed the control group, and their average age was 6.5 ± 2.4 years. For patients with NS, their body weight according to height had increased an average of 8.4% in comparison to the controls. The patient and control group demographics and clinical characteristics are shown in Table 1.

Systolic blood pressure did not significantly differ between the control and NS patient groups, but diastolic blood pressure values were significantly higher in the NS patients (P < 0.05). No difference was identified between the NS patients and controls for heart rate or IVCI (P > 0.05). The values for the IVCCI in the NS patients were much lower than the values calculated for the control subjects (P < 0.05, Table 2). Hypervolemia was identified in 65% of the NS patients as the relative fluid load was higher than 15%, and 35% of the NS patients were found to be normovolemic with relative fluid loads of 5%–15% identified via bioimpedance analysis. Hypovolemia

was not identified in any NS patients. By comparing bioimpedance results between the controls and the NS patients, it was found that this method has a sensitivity of 65% and a specificity of 90%.

When the clinical signs of edema were evaluated, patients with NS were divided into 2 groups depending on the distribution of edema: localized and generalized edema (Table 3). The IVCI was higher in patients with generalized edema as compared to patients with localized edema (P < 0.05). No significant differences were found between patients with localized and generalized edema in regards to IVCCI (P > 0.05). The relative fluid load was elevated in patients with generalized edema in contrast to patients with localized edema (P < 0.05). By determining volume load via IVCI, it was found that the sensitivity was 87% and the specificity was 50%. Using the IVCCI to determine volume load, the sensitivity was 95% and the specificity was 10%. However, the sensitivity of bioimpedance was found to be 83% and the specificity was found to be 80%.

Table 1. Demographics and clinical characteristics.

	NS patients (n = 34)	Controls (n = 20)
Age (years)	7.57 ± 2.25	6.5 ± 2.4
Sex, female/male (n/n)	11/23	10/10
Weight (kg)	28.7 ± 15.3	25.8 ± 12.2
Weight according to height (kg)	26.5 ± 15.3	25.3 ± 11.2
Height (cm)	121.3 ± 24.2	123.6 ± 24
Body mass index (kg/m ²)	18.3 ± 2.4	17.5 ± 2.6
Dyspnea or orthopnea (n)	2	0
Hepatomegaly (n)	6	0
Jugular vein distension (n)	6	0

Table 2. Volume status measurements.

	NS patients	Controls	P-value
Blood pressure (mmHg)			
≥95th percentile	n = 9		
<95th percentile	n = 25	n = 20	
Systolic	104 ± 14.9	100.5 ± 9.4	>0.05
Diastolic	69.9 ± 13.3	49 ± 8.7	<0.05
Cardiothoracic index	0.46 ± 0.04	0.46 ± 0.03	>0.05
Inferior vena cava index (cm/m ²)	0.66 ± 0.33	0.60 ± 0.3	>0.05
Inferior vena cava collapsibility index (%)	39.4 ± 8.6	56.9 ± 8.7	<0.05
Relative fluid load (%)	18.2 ± 10.4	6.8 ± 1.3	
≥15 (hypervolemia)	n = 22	n = 2	<0.05
<15 (normovolemia)	n = 12	n = 18	

Table 3. Volume status comparison according to edema type.

	Localized edema n = 10	Generalized edema n = 24	P-value
Inferior vena cava index (cm/m ²)	0.55 ± 0.31	0.71 ± 0.30	
>0.50	n = 5	n = 21	<0.05
<0.50	n = 5	n = 3	
Inferior vena cava collapsibility index (%)	38.8 ± 10.1	39.6 ± 8.09	
<50	n = 9	n = 23	>0.05
>50	n = 1	n = 1	
Relative fluid load (%)	8.5 ± 5.7	22.3 ± 9.2	
≥15 (hypervolemia)	n = 2	n = 20	<0.05
<15 (normovolemia)	n = 8	n = 4	

4. Discussion

In children between the ages of 2 and 6, steroid-sensitive NS is most often diagnosed, and edema is one of the most common clinical presentations. The pathogenesis of the development of edema is still debated, and 2 different mechanisms have been proposed (17). According to the underfill theory, NS patients initially are hypovolemic, which triggers water and sodium reabsorption secondary to renin-angiotensin-aldosterone system activation. Conversely, the overfill theory has also been proposed, which posits that hypervolemia arising from water and sodium reabsorption in the kidneys causes edema (18,19). Many previously published studies evaluating volume overload in NS patients have used these theories to explain the development of edema.

In our study, clinical symptoms and laboratory results were utilized to evaluate the volume status of NS patients. The volume load was determined clinically by determining blood pressure and the presence of tachycardia, dyspnea, orthopnea, hepatomegaly, edema, and jugular vein distension (20). The average increase in weight relative to height was 8.4% in NS patients, and of the patients that had generalized edema (n = 24), there were 2 patients with dyspnea and 6 patients with hepatomegaly and jugular distension. The IVCI is a good indicator of circulating blood volume, and the IVCCI is an accurate determinant of right atrial pressure (21). Echocardiography, IVCI, and IVCCI are utilized in adult patients as these techniques are noninvasive and help determine intravascular volume load (22). In all, these techniques are reliable and relatively easy to perform. However, these techniques can be difficult to carry out on pediatric patients, which increases the possibility of obtaining inaccurate measurements, especially for patients with cardiac insufficiency and/or heart disease. Major variations may be observed depending on the individual performing the technique, making it difficult to obtain any useful information regarding the severity of volume overload (23).

In a study by Ghaffari et al., IVCI and IVCCI measurements were performed to determine the volume status of 30 pediatric patients without edema, 13 patients with moderate edema, and 11 patients with significant edema. The IVCI was found to be higher in patients without edema, and IVCCI values were similar between all groups. In this study, echocardiography had limited utility in determining volume status, particularly for pediatric patients with severe volume overload (24). However, in our study, IVCI and IVCCI measurements were performed with echocardiography for all patients. We found that IVCCI values were lower in children with NS when compared with the controls. In contrast, values for the IVCI were similar between the NS patients and the controls.

When patients with localized edema were compared with patients with generalized edema, the IVCI was significantly higher in children with generalized edema as opposed to children with localized edema (P < 0.05). No significant difference was identified in IVCCI values between patients with generalized and localized edema (P > 0.05). Our IVCI and IVCCI findings are comparable to reports in the literature, but the extent of the edema cannot be determined by IVCCI alone because patients with localized and generalized edema had similar IVCCI values. Our data suggest that IVCCI only reveals the presence of edema, but this measurement gives no indication of edema severity. This is reflected by the low specificity that we calculated for the IVCCI in determining volume status at 10%. We also found that volume load was 95% according to the IVCCI.

Determining OH and relative fluid load (OH/ECF) with BIS is another method that is frequently used to determine volume status, mainly in patients receiving hemodialysis (25,26). Wabel et al. determined the relationship between blood pressure and OH in a study that compared ECF volume between 1244 control subjects with OH and 500 hemodialysis patients (16). In another study including 269

subjects by Wabel et al., it was found that patients with a relative fluid load of greater than 15%, also known as hypervolemia, had higher mortality rates over a 3.5-year follow-up period (27).

There have been a few studies that evaluated volume load with BIS in pediatric patients with NS. To date, however, there have been no studies that compared the efficiency of bioimpedance with echocardiographic measurements in children with NS. In our study, OH and relative fluid load measurements were performed by BIS in all patients. The average OH value was 1.42 ± 1.1 L and the average relative fluid load was $18.2 \pm 10.4\%$. The relative fluid load was significantly higher in patients with generalized edema than in patients with localized edema. When assessing bioimpedance and clinical findings, it was found that bioimpedance had a sensitivity of 83% and a specificity of 80% regarding the presence and severity of volume overload. Therefore, these data suggest that bioimpedance may be used to measure volume status and may provide more accurate results than echocardiography.

Left atrial diameter and total body water were measured by IVCCI and BIS to investigate the pathogenesis of edema in children with steroid-sensitive NS. In a study conducted

by Gurgoze et al., it was found that total body water was significantly higher in patients with edema. Comparing patients with and without edema, it was determined that their left atrial diameter and IVCCI values were similar. Moreover, patients with NS tended to be normovolemic instead of being hypovolemic (28). ANP and cGMP are biomarkers used to determine volume load for patients with conditions such as cardiac valve diseases and congestive heart failure affecting the left atrium. Obtaining these biomarkers requires complex and invasive techniques that are also expensive, which restricts their regular use in clinical settings.

Overall, BIS provides more accurate results in determining volume status in children with NS when compared with echocardiography. Moreover, BIS is easily performed and demonstrates less variability due to performer skill differences. Our data suggest that BIS may be a superior technique to echocardiography since the sensitivity and specificity of BIS is relatively higher. In all, BIS is cost-effective and may be more reliable than echocardiography when determining volume load in children with NS.

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