Bioimpedance-based volume overload at clinical target weight is negative in hemodialysis patients with a high body mass index

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**Abstract**

Objective: To compare volume overload in stable hemodialysis (HD) patients assessed by standard clinical judgment with data obtained from bioimpedance analysis.

Methods: Ultrafiltration volume ($V_U$) was delivered as prescribed by standard clinical practice. Independently, a measure for volume overload was assessed by a clinical score ($S_W$). The Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) was used to derive values for extracellular volume ($V_E$) and volume overload ($V_O$) before HD. Arterial pressures ($P_0, P_1$) and serum levels of NT-pro-BNP ($B_0, B_1$) were evaluated before and after HD.

Results: In 28 patients (11 women, age: 51.3±13.3 y, body mass index, BMI: 18.5 to 40.9 kg/m²; $V_E$ 17.91±3.45 L) delivered $V_U$ was 2.41±1.03 L and not different from $V_O$ of 2.08±1.49 L derived from bioimpedance analysis. There was no correlation between $V_O$ and $V_U$ ($r=-0.15, p=0.46$) but a negative correlation between the difference $V_O-V_U$ (i.e. the volume overload at treatment end) and BMI ($r=-0.49, p<0.01$). Positive correlations were observed between $B_0$ and the relative volume overload ($=V_O/V_E$) ($r=0.58, p<0.001$).

Conclusion: The well recognized relationship between cardiac natriuretic peptides and volume expansion was confirmed. The volume overload at treatment end ($V_O-V_U$) was negligible for the whole group of patients but more negative with increasing BMI. It therefore appears that in comparison to bioimpedance-based evaluation the clinical judgment overestimates volume overload in obese patients which leads to the delivery of high ultrafiltration volumes and to volume contraction at the end of a dialysis session in this group of patients. (250 words)

Keywords: bioimpedance – body mass index – natriuretic peptide – ultrafiltration
Introduction

Volume overload and hypertension are known to importantly contribute to high cardiovascular morbidity and mortality seen in dialysis patients [1, 2]. The correct assessment of volume status is especially demanding as only a small increase in extracellular volume over prolonged periods of time is assumed to lead to considerable cardiac strain and, as a consequence, to left ventricular hypertrophy [3, 4]. In clinical practice volume overload is most often judged by clinical signs such as edema, dyspnea, hypertension, or coughing. It is obvious that such an assessment is subject to many limitations because these symptoms are not specific for volume status. To overcome these limitations, alternative and more objective methods have been suggested. For example, the diameter and collapsibility of the vena cava measured by ultrasonography is assumed to provide information on intravascular volume [5, 6, 7]. Pulmonary congestion seen in the chest X-ray offers another possibility to detect fluid overload [3, 8]. And the N-terminal fragment of B-type natriuretic peptide (NT-pro-BNP) has been proposed as a serologic biomarker of volume overload. But these methods have their own limitations, they are time consuming and/or they are not readily available at the bedside. As of today bioimpedance analysis appears to be the most promising technique for a simple, user-friendly, standardized, and objective assessment of patient volume status to be used with every treatment [9, 10, 11, 12, 13]. With this technique it is not only possible to estimate the patient’s fluid status with sufficient accuracy but to obtain information on body composition and nutritional aspects as well [9, 10, 14]. Recent studies have shown that information derived from bioimpedance analysis is useful to improve the fluid management in dialysis patients, to save antihypertensive medication, and to reduce the frequency of intradialytic adverse events [15]. In spite of these promising results there is an ongoing discussion regarding the reliability and the clinical value of bioimpedance analysis in clinical practice. Volume assessment is especially difficult in obese subjects where the distribution of adipose tissue affects bioelectric measurements and where increased skin turgor conceals volume depletion assessed by clinical judgment.

The aim of this study therefore was to compare the clinical assessment to the volume status measured by a new bioimpedance device in everyday practice in a
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group of patients with a wide range of body mass indices. Additionally, the relationships between clinical, bioelectrical, and serological measures of volume overload were assessed.
Material and Methods

Subjects

Twenty-eight prevalent stable hemodialysis patients from the dialysis unit of the University Medical Center Graz provided written informed consent to participate in this study. The study protocol was approved by the local Ethics Committee of the Medical University Graz. Subjects with pacemakers and patients with major amputations of extremities were excluded.

Bioimpedance

Fluid status was assessed using the Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) measuring so-called whole body bioimpedance at 50 frequencies within the range of 5 kHz to 1 MHz. Measurements were done in supine body position after a 5 min of rest as specified by the manufacturer. Current injection and voltage sensing electrodes were placed on the wrist and the ankle of the contra-lateral access side of the body. Measurements were performed immediately before a midweek dialysis session. Total body water (VT), extracellular (VE) and intracellular water volumes (VI) were derived from bioimpedance data and the volume overload (VO) was then calculated by the BCM device, using the proprietary body composition model as described elsewhere [14, 16, 17].

Parameters

In all patients the body mass index (BMI) was recorded before treatment. Weight, arterial blood pressures (P0, and P1, respectively), and serum levels of NT-pro-BNP were determined before and after hemodialysis (B0, and B1, respectively). NT-pro-BNP was measured by immunoassay (ECLIA Roche Diagnostics GmbH, Mannheim, Germany).

In all patients the volume status was assessed according to the clinical volume score (SW) developed by Wizemann and Schilling [18]. In a questionnaire clinical signs of volume expansion (i.e. different stages of pretibial edema formation, dyspnea, chronic coughing, rising blood pressure during ultrafiltration) as well as signs of volume depletion (i.e. presence of thirst, varying degrees of symptomatic hypotension, muscle cramps, dizziness and fatigue between dialysis sessions) are recorded and scored. A positive sum of
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the scored symptoms indicates volume expansion while a negative sum indicates volume depletion.

Treatment settings such as blood flows and dialysate compositions as well as the removal of excess volume by ultrafiltration were delivered as prescribed without adjustment. Delivered ultrafiltration volumes ($V_U$) were recorded.

Statistical analysis

Pearson’s correlation coefficients were determined for variables $B_0$, $B_1$, $V_O$, $V_U$, $V_O/V_E$ and $S_W$. $\chi^2$- and two-sided $t$-tests were used to assess differences among groups. For all tests, the significance level was set at 5%. Statistical calculations were done with SPSS, Version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).
Results

Twenty-eight patients (11 women, 51.3±13.3 years) were studied (Tab. 1). The mean arterial pressure before dialysis ($P_0$) was 102.6±15.5 mmHg and significantly correlated with the clinical volume score ($W_S$) ($r=0.44$, $p<0.05$). Mean arterial pressure after dialysis ($P_1$) significantly fell to 93.1±17.9 mmHg ($p<0.01$).

The ultrafiltration volume effectively removed ($V_U$) determined from the difference between pre- and post-dialysis body mass was 2.4±1.0 L and 0.45±0.16 L larger than the ultrafiltration volume prescribed according to the patient’s target body mass. This small difference was most likely due to a systematic overestimation of fluid ingested during dialysis and/or the amount of fluid required to rinse the blood from the extracorporeal circulation. However, both volumes where highly correlated ($r=0.99$, $p<0.001$) and the ultrafiltration volume effectively removed ($V_U$) was used for further analysis. This volume was not different from the mean volume overload ($V_O$) of 2.08±1.49 L obtained from bioimpedance analysis ($p$=n.s., $t$-test). Bland-Altman analysis showed a small bias of -0.33 L for the difference ($V_O-V_U$), albeit with considerable limits of agreement (-4.2 to 3.5 L) (Fig. 1). In spite of this small bias determined for the whole group there was no correlation between $V_U$ and $V_O$ in individual studies ($r=-0.13$, $p=0.51$). There was a positive correlation between $V_U$ and BMI ($r=0.47$, $p<0.01$) and a negative correlation between $V_O$ and BMI ($r=-0.31$, $p=0.12$). Thus, the difference ($V_O-V_U$) was also significantly correlated to BMI ($r=0.49$, $p<0.01$) (Fig. 2). BMI was significantly correlated to body mass ($r=0.91$, $p<0.001$) so that high BMI was due to high mass and not to small stature.

Post-dialysis blood pressures ($P_1$) as well as the drop in arterial pressures ($P_0$-$P_1$) were negatively correlated to ultrafiltration volume $V_U$ ($P_1$: $r=-0.43$, $p<0.05$; $P_0$-$P_1$: $r=-0.59$, $p<0.001$) and positively correlated to post-dialysis volume overload $V_O$-$V_U$ ($P_1$: $r=0.44$, $p<0.05$; $P_0$-$P_1$: $r=0.41$, $p<0.05$). Post-dialysis pressure $P_1$ was negatively correlated with body mass $M_b$ ($P_1$: $r=-0.41$, $p<0.05$) and BMI ($P_1$: $r=-0.52$, $p<0.01$).

Predialytic NT-pro-BNP levels ($B_0$) were negatively correlated with body mass ($r=-0.31$, $p<0.05$) and positively correlated with relative volume overload
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\( V_0/V_E \) \( (r=0.58, \ p=0.001, \ \text{Fig. 3}) \). Last, but not least, NT-pro-BNP levels significantly dropped during dialysis \( (p<0.05) \).
Discussion

The main observations of this study are: a) There was a close correspondence between estimated volume overload obtained from bioimpedance analysis $V_O$ and ultrafiltration volume $V_U$ for the whole group of patients, albeit with wide limits of agreement; b) at the same time, there was no correlation between $V_O$ and $V_U$ in individual patients; and c) there was a negative correlation between this discrepancy quantified as $V_O - V_U$ with body mass index.

The negligible bias between estimated volume overload and ultrafiltration volume is in support of the null-hypothesis that for the whole group of patients volume overload was adequately removed as prescribed by routine clinical practice. This result therefore appears to be in support of bioimpedance measurements and model calculations provided by the BCM. The limits of agreement, however, were wide, presumably because of the large range in body mass and BMI of the study population (Tab. 1). Thus, the comparison of $V_O$ and $V_U$ requires a more careful analysis.

In individual studies, there was no relationship between $V_O$ and $V_U$, and the reason for this discrepancy can be attributed to errors in the prescription of $V_U$ according to clinical routine and/or to errors in the estimation of $V_O$ by bioimpedance analysis. Indeed, the BCM has been validated for subjects with a BMI between 18 and 32 kg/m$^2$, and volume estimates in patients with a BMI outside that range are therefore uncertain. On the other hand, there was only a slight trend for $V_O$ to decrease as BMI increased in this study. It therefore appears as if BCM predictions could be extended into the higher BMI range. Others have observed that volumes derived from so-called whole-body bioimpedance measurements are more variable in obese subjects and the question therefore arises whether segmental measurements should be preferred in this setting [19, 20, 21]. Part of the variability in obese subjects is most likely due to the different contribution of adipose tissue on whole-body bioimpedance depending on its distribution between the trunk (visceral, central fat) and the limbs (peripheral fat). This effect is comparable to the different contribution of extracellular fluid on whole-body bioimpedance whether it is located in the trunk or in the limbs [22]. It has been shown that the redistribution of fluid between the trunk and the limbs affects the measurement and the interpretation of so-
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called whole bioimpedance data [23, 24, 25] and for this reason an immediate measurement before dialysis treatment is recommended by the manufacturer of the BCM. The fluid shifts between body segments probably also explain the differences in post-dialysis bioimpedance seen after long 8 h treatments where fluid is allowed to equilibrate across the body compared to regular 4 h treatments where such equilibration is more likely incomplete [26].

\(V_U\) was observed to increase with BMI which is plausible, as larger patients tend to accumulate more volume. Therefore, the difference \(V_O-V_U\) significantly decreased with increasing BMI. The difference \(V_O-V_U\) refers to the volume overload at the end of dialysis, a positive value representing a (positive) volume overload, and a negative value representing a volume deficit, respectively. A (positive) volume overload at the end of dialysis is not so surprising because of the well known difficulties to remove excess fluid volume from the patient during hemodialysis for hemodynamic reasons [27]. More surprising, however, is the negative correlation of volume overload with increasing BMI. In fact, at very high BMI the difference \(V_O-V_U\) was always negative in our study. Especially in obese patients the clinical assessment seems to overestimate patient volume status thus leading to high ultrafiltration and consequently to volume depletion at the end of a dialysis session. One can argue that the standard clinical assessment of volume to be removed by ultrafiltration was inaccurate because of limitations mentioned above. This assumption is confirmed by the poor correlation found between bioimpedance measures and the clinical score in this cross-sectional analysis. The negative correlation between post-dialysis blood pressure \(P_1\) with body mass \(M_b\) and BMI also indicates that more volume was removed in large patients than that required to reach the same blood pressure in the whole study group.

Part of the overestimation, however, is inherently linked to body size. It is clear that - everything else being equal - the large patient is less susceptible to a given volume overload or volume contraction compared to the small patient, essentially because the capacity to buffer the same volume perturbation increases with body size. Therefore, if volume removal is for example prescribed to attain the same blood pressure, more volume is automatically removed in the large patient. As current clinical practice attempts to remove as much volume as
possible, the large patient is more likely to be volume contracted compared to the BCM estimate. This approach, however, is in debate [28, 29].

Consistent with the well-known fact that elevated cardiac natriuretic peptides reflect volume expansion [30, 31, 32, 33] we found a positive relationship between predialytic NT-pro-BNP levels and the estimated pre-dialysis volume overload $V_0$. NT-pro-BNP levels significantly decreased during dialysis and ultrafiltration. This decrease cannot exclusively be tied to the improved volume situation because NT-pro-BNP is also cleared with high-flux dialysis. As NT-pro-BNP is affected by other factors beyond volume expansion, it fails to be a reliable tool for assessing patient dry mass. For example, it was recently shown that elevated NT-pro-BNP concentration was also related to malnutrition [34]. In our study, NT-pro-BNP concentration in obese patients was inversely related to body mass, supporting the existence of such a relationship and the hypothesis of inverse epidemiology regarding obesity in dialysis patients. This observation is also consistent with our finding that at the end of dialysis obese patients appeared to be volume contracted compared to the BCM estimate.

A limitation of the present study is of course the small number of patients and the lack in statistical power. On the other hand, bioimpedance analysis was tested in a standard clinical setting thus providing practical information for everyday routine.

In conclusion, the well recognized relationship between cardiac natriuretic peptides and volume expansion was confirmed. In addition, there was no significant difference between clinically-based and bioimpedance-based volume assessment in the whole group of patients. However, there was a large discrepancy between clinically- and bioimpedance-based estimates in individual patients depending on BMI. At the end of dialysis obese patients appeared to be volume contracted compared to the BCM estimate. The clinical implications of this observation remain to be elucidated in future and larger studies.
Conflict of interest

None to declare.
Disclosure

This work originated from a diploma thesis [35] and part of it has been presented and published in abstract form at the Annual Meeting of the Austrian Society of Nephrology, Oct. 2-3, in Graz, Austria [36], and at the XVII ERA-EDTA Congress – II DGfN Congress, June 25–28, 2010, in Munich, Germany [37].
Acknowledgement

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Bland-Altman analysis for volume overload $V_O$ and ultrafiltration volume $V_U$ comparing the difference ($V_O - V_U$) to the average of both measures. The mean difference is indicated by the full line, the limits of agreement ($\pm 2$ SD) are given by the broken lines ($n=28$).
Fig. 2

Volume overload and body mass index

Difference between volume overload and ultrafiltration volume ($V_O - V_U$) (i.e., the volume overload at the end of dialysis) plotted vs. body mass index BMI. The broken line shows the linear regression given as $y = 3.90 - 0.16x$; $r^2 = 0.24$, $p < 0.01 (n = 28)$. 
**Fig. 3**

NT-pro-BNP and volume overload

Correlation between predialytic levels of NT-pro-BNP and the relative predialytic volume overload ($V_O/V_E$): $r^2=0.58; p\leq0.001$; line of linear regression (dotted line).
**Tab. 1**

Patient and treatment characteristics in presented in the order of increasing BMI (n=28)

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<td>3.5</td>
<td>-2.7</td>
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<td>258</td>
<td>165</td>
</tr>
<tr>
<td>122.0</td>
<td>38.2</td>
<td>100.0</td>
<td>74.7</td>
<td>26.0</td>
<td>1.2</td>
<td>4.8</td>
<td>-3.6</td>
<td>4.6</td>
<td>965</td>
<td>619</td>
</tr>
<tr>
<td>107.6</td>
<td>40.8</td>
<td>97.3</td>
<td>75.0</td>
<td>19.6</td>
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<td>-3.8</td>
<td>-2.6</td>
<td>833</td>
<td>1019</td>
</tr>
</tbody>
</table>

Abbreviations: number of subjects, n; predialytic body mass, M₀; body mass index, BMI; pre- and post-dialytic mean arterial pressures, P₀, P₁; extracellular volume, Vₑ; volume overload V₀; relative volume overload, V₀/Vₑ; delivered ultrafiltration volume, Vᵤ; pre- and post-dialytic NT-pro-BNP, B₀, B₁; clinical
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score according to Wizemann et al., Sw; *p<0.05 (post- compared to pre-dialytic values)
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