Simple estimation of excess fluid volume in hemodialysis patients based on multifrequency bioelectrical impedance analysis data

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Abstract To develop a novel index of body water distribution status in hemodialysis (HD) patients, we derived equations that estimate the excess fluid volume (ExFv) in HD patients, and evaluated their applicability. The ExFv estimation equations were derived based on the correlations between extracellular water (ECW) and total body water (TBW) volumes of healthy adults, which were measured using multifrequency bioelectrical impedance analysis. Here, the effect of increasing ECW/TBW with age was corrected. The estimated ExFv and the circulatory and body fluid status of HD patients were compared between two groups of 20 patients with dry weight (DW) and 16 patients with overhydration (OH), both of which were clinically classified. The indices of circulatory and body fluid status were significantly higher in the OH group than in the DW group. The ExFv values of the DW and OH groups were 0.06 ± 0.19 L and 0.78 ± 0.32 L in males and 0.06 ± 0.16 L and 0.51 ± 0.18 L in females, respectively, indicating significantly higher values in the OH group. The derived ExFv estimation equations allow us a simple and quantitative assessment of the body water distribution status in HD patients.

Keywords dry weight, excess fluid volume, extracellular water, hemodialysis, multifrequency bioelectrical impedance analysis, total body water

Introduction

A multifrequency bioelectrical impedance analysis (MF-BIA) enables the estimation of extracellular water (ECW) volume and total body water (TBW) volume based on the body’s electrical resistance according to electrical currents measured at a low frequency for ECW and high frequency for TBW [1], and there are some previous studies on application of MF-BIA data to setting dry weight (DW) of hemodialysis (HD) patients [2–5].

Previously, other groups used either a correlation between ECW and body weight [4] or another correlation between ECW/TBW and age [5] of healthy subjects for setting DW of HD patients. However, none of the previous methods demonstrated sufficient accuracy for estimating DW of HD patients because of the influences of body shape and body fat [4, 5].

Recently, we reported that strong correlations between ECW and TBW measured by MF-BIA in healthy adults (ECW–TBW correlation equations) ranging from lean to moderate obese and that the differences between the measured ECW and the predicted ECW from the ECW–TBW correlation equations increased with age [6]. It is also suggested that the characteristics of body water distribution obtained by MF-BIA in healthy adults be an index to evaluate the DW in HD patients [6].

In this study, to develop a novel index of body water distribution status in HD patients, we derived simple equations to estimate the excess fluid volume (ExFv) in HD patients based on the body water distribution of healthy adults measured by MF-BIA (ExFv estimation equations) and examined their clinical applicability to HD patients’ data.
Methods

Subjects

The clinical applicability of the ExFv estimation equations were investigated retrospectively on 36 HD outpatients undergoing 4-h HD sessions three times a week. The patients had also undergone DW assessment previously (18 males and 18 females; mean age: 67.0 ± 10.4 years) (Table 1).

The protocol for this study was approved by the ethics committee of the Kurashiki Central Hospital (approval number: 2229).

Measurement of Body Composition by MF-BIA

The body composition of HD patients was measured using an MF-BIA-based segmental body composition analyzer (InBody® S20; InBody Japan Inc., Tokyo, Japan). The analyzer measured the electrical resistance across five body segments (arms, trunk, and legs) via tactile electrodes placed at eight body locations at six frequencies (1, 5, 50, 250, 500, and 1,000 kHz), with body water volumes being estimated. Basic physical data of each HD patient, including height, age, and sex, were entered into the analyzer. After resting for more than 10 minutes following an HD session, the body weight, body mass index (BMI [kg/m²]), intracellular water (ICW [L]), extracellular water (ECW [L]), total body water (TBW [L]), ECW/TBW [ ], percentage of body fat mass [%], and fat-free mass [kg] of each HD patient in a supine position were measured.

Evaluation Indices of Circulatory and Body Fluid Status in HD Patients

The relative change in the circulating blood volume (%BV [%]) of HD patients was measured using a continuous hematocrit monitor (CRIT-LINE®; Fresenius Medical Care, Bad Homburg, v.d.H., Germany) in the same HD session as the body composition analysis by MF-BIA. The %BV was continuously measured from 5 minutes after HD onset until the end of HD by a sensor attached to the arterial chamber located before a hemodialyzer. The volume index (VI [(%h)/(mL/h/kg)]), an index of circulatory and body fluid status reflecting the plasma refilling level, was calculated from the following equation using the %BV and body weight at the end of HD, HD time, and ultrafiltration volume [7] (Eq. 1).

\[
\text{Volume index (VI)} = \frac{\%BV}{\text{HD time} \times \left( \frac{\text{ultrafiltration volume}}{\text{HD time} \times \text{post-HD body weight}} \right)}
\]

Systolic (S-BP [mmHg]) and diastolic blood pressure (D-BP [mmHg]) were measured once every hour from the start until the end of HD during the same HD session as that for the %BV measurement. As additional indices of body fluid status, the post-HD X-ray cardiothoracic ratio (CTR [%]) and brain natriuretic peptide (BNP [pg/mL]) were measured using regular laboratory and physiological tests, which were conducted in the same month as the body composition measurement.

Derivation and Clinical Applicability of the ExFv Estimation Equations in HD Patients

First, we derived the ExFv estimation equations based on the results of previous our report [6]. And then, to evaluate the clinical applicability of ExFv calculated from the ExFv estimation equations, the ExFv values of HD patients were compared between the two clinical states of DW (DW group) and overhydration (OH group).

Based on the guidelines of the Japanese Society for Dialysis Therapy, CTR and blood pressure were used as the criteria for the clinical DW and OH groups [8]. In addition, VI was also used to evaluate the OH status [7]. The HD patients satisfying the following three criteria without edema and blood pressure reduction during HD were categorized into the DW group [7, 8]:

1) CTR ≤ 50% (for male) or ≤ 53% (for female)
2) S-BP (pre-HD) < 140 mmHg and D-BP (pre-HD) < 90 mmHg
3) VI ≤ –0.22 (%h)/(mL/h/kg)

Furthermore, the HD patients satisfying the following three criteria without edema were categorized into the OH group [7, 8]:

1) CTR > 50% (for male) or > 53% (for female)
2) S-BP (pre-HD) ≥ 140 mmHg
3) VI > –0.22 (%h)/(mL/h/kg)

In addition to the ExFv, the indices of circulatory and

| Basal disease                        | Male HD patients (n = 18) | Female HD patients (n = 18) |
|--------------------------------------|--------------------------|-----------------------------|
| Chronic glomerulonephritis           | 5                        | 11                          |
| Diabetic nephropathy                 | 4                        | 2                           |
| Polycystic kidney                    | 1                        | 1                           |
| Nephrosclerosis                      | 1                        | 2                           |
| Rapidly progressive glomerulonephritis| 3                        | 0                           |
| IgA nephropathy                      | 3                        | 1                           |
| Other disease                        | 1                        | 1                           |

HD: hemodialysis
Data Analyses

All statistical analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Student’s t-test was used to compare the mean value of data between the two groups. All data were presented as mean ± standard deviation (SD), and p < 0.05 was considered statistically significant.

Results

Derivation of the ExFv Estimation Equations in HD Patients

Based on the data on healthy adults in our previous report [6], we first derived the “ideal” ECW (i-ECW) of HD patients from TBW and age.

\[
i-ECW_{m} = (0.365 \times TBW_{m} + 0.581) + (0.011 \times age – 0.609) \quad (2)
\]

\[
i-ECW_{f} = (0.384 \times TBW_{f} + 0.088) + (0.006 \times age – 0.361) \quad (3)
\]

Furthermore, the ExFv estimation equations for HD patients (Eqs. 4 and 5) were derived as the difference between the measured ECW and the i-ECW estimated by Eqs. 2 and 3. In other words, when TBW and age are the same between HD patients and healthy subjects, the ExFv estimation equations should derive the gap of ECW between the two groups, assuming ECW is identical both in HD patients with appropriate DW and in healthy subjects.

\[
ExFv_{m} = ECW_{m} – i-ECW_{m} = ECW_{m} – (0.365 \times TBW_{m} + 0.581) – (0.011 \times age – 0.609) \quad (4)
\]

\[
ExFv_{f} = ECW_{f} – i-ECW_{f} = ECW_{f} – (0.384 \times TBW_{f} + 0.088) – (0.006 \times age – 0.361) \quad (5)
\]

Comparison of Body Composition and Evaluation Indices of Circulatory and Body Fluid Status Between the DW and OH Groups

The body composition and the evaluation indices of circulatory and body fluid status of the DW and OH groups are shown in Table 2. Twenty patients (10 males and 10 females; mean age: 67.4 ± 9.4 years) were classified in the DW group and 16 patients (8 males and 8 females; mean age: 66.5 ± 11.8 years) in the OH group (p = N.S. vs. DW group). Although height, body weight, ICW, ECW, TBW, and fat-free mass were significantly higher in the male HD group than in the female HD group, there were no significant differences between the DW and OH groups in both males and females. In contrast, the ECW/TBW did not differ significantly between the male and female HD patients, despite the ECW/TBW of the OH group being significantly higher than that of the DW group in both males and females (p < 0.001). Although there were no significant differences in the fat mass and %fat mass between both males and females, these indices tended to be lower in the OH group than in the DW group. In addition, no significant differences in ultrafiltration volume and ultrafiltration rate were observed between the DW and OH groups for both males and females.

The VI, pre- and post-HD S-BP, and CTR of the OH group in both males and females were significantly higher than those of the DW group. Additionally, the BNP of the OH group in both males and females tended to be higher than that of the DW group, with a significant difference observed in females (p < 0.05).

The ExFv values of the DW group were 0.06 ± 0.19 L in males and 0.06 ± 0.16 L in females, both of which were nearly zero. In the OH group, the ExFv values were 0.78 ± 0.32 L in males and 0.51 ± 0.18 L in females, both of which were significantly higher than those of the DW group (p < 0.001 vs. DW group) (Table 2).

Discussion

In this study, we derived the ExFv estimation equations for HD patients based on the ECW–TBW correlation equations in healthy subjects with the age effect being incorporated. We confirmed that the “estimated ExFv” calculated from the estimation equations was nearly zero in the clinical DW group and significantly higher in the OH group.

Comparison of Body Composition and Evaluation Indices of Circulatory and Body Fluid Status Between the DW and OH Groups

There was no significant difference in age between the DW and OH groups for both males and females, and thus it was considered that the increase of ECW/TBW with aging [5, 9] did not affect the evaluation indices of circulatory and body fluid status in both groups. Furthermore, there were no significant differences between the two groups in height and weight, which could affect the values of body composition measured by MF-BIA [1]. However, in the OH group of both males and females, %fat mass and BMI tended to
be lower because of the large value of fat-free mass and the low value of fat mass. This result suggests that malnutrition cause an increase of ExFv in HD patients observed in the present study, which is consistent with our previous report [9]. On the other hand, it is considered that the evaluation indices of circulatory and body fluid status in both the DW and OH groups of males and females were not affected by HD itself, because there were no significant differences in the ultrafiltration volume and ultrafiltration rate between the two groups (Table 2).

The %BV, VI, S-BP (pre- and post-HD), and CTR, all of which are the evaluation indices of circulatory and body fluid status, were significantly higher in the OH group than in the DW group in all HD patients. In addition, the BNP of the OH group tended to be higher for both males and females; however, the measured BNP values showed large deviations, and thus, there was a significant difference in BNP only in female HD patients (Table 2). Because BNP has been reported to be affected by basal diseases such as heart failure [10], measured BNP values may exhibit large variability. In this study, we did not examine possible influences of cardiac function and complications of the subjects on the BNP. However, because the evaluation indices of circulatory and body fluid status (%BV, VI, S-BP, and CTR) other than BNP were significantly higher in the OH group than in the DW group, the classification criteria between the clinical DW and OH groups used in the current study were able to distinguish the circulatory and body fluid status of both groups with significant differences.

### Characteristic and Clinical Applicability of ExFv as an Index for Body Water Distribution

Chamney et al. developed a method for setting the DW of HD patients by reducing excessive ECW to match the association between ECW and body weight of HD patients to that of healthy subjects based on the strong positive correlation between ECW and body weight of healthy subjects.

### Table 2 ExFv, body composition, and evaluation indices of circulatory and body fluid and nutritional status in DW and OH groups

| Measurement data | Male HD patients (n = 18) | Female HD patients (n = 18) |
|------------------|--------------------------|---------------------------|
|                  | DW group (n = 10) | OH group (n = 8) | p-value | DW group (n = 10) | OH group (n = 8) | p-value |
| ExFv [L]         | 0.06 ± 0.19 | 0.78 ± 0.32 | <0.001 | 0.06 ± 0.16 | 0.51 ± 0.18 | <0.001 |
| Age [years]      | 68.9 ± 7.5  | 62.3 ± 14.7 | 0.272  | 65.8 ± 11.1 | 70.8 ± 6.3 | 0.253  |
| Height [cm]      | 164.9 ± 4.7*** | 167.8 ± 4.1††† | 0.176 | 153.5 ± 5.6 | 151.1 ± 5.2 | 0.355 |
| Body weight [kg] (pre-HD) | 59.4 ± 8.7*  | 55.1 ± 5.6†† | 0.224 | 49.2 ± 10.6 | 44.7 ± 5.7 | 0.262 |
| Body weight [kg] (post-HD) | 56.9 ± 8.7* | 53.1 ± 5.4†† | 0.265 | 47.3 ± 10.2 | 42.7 ± 5.5 | 0.241 |
| BMI [kg/m²]      | 20.9 ± 2.3  | 18.9 ± 1.6  | <0.05  | 20.1 ± 4.6  | 18.7 ± 1.7 | 0.371  |
| Ultrafiltration volume [L] | 2.5 ± 0.3* | 2.1 ± 0.9 | <0.227 | 0.06 ± 0.19 | 0.78 ± 0.32 | <0.001 |
| Ultrafiltration rate [%] | 4.3 ± 0.8 | 3.7 ± 1.7 | 0.415 | 4.0 ± 0.8 | 4.1 ± 1.0 | 0.299 |
| ICW [L]          | 18.4 ± 2.6** | 19.2 ± 2.3†† | 0.502 | 14.9 ± 2.5 | 15.1 ± 2.0 | 0.873 |
| ECW [L]          | 11.8 ± 1.4** | 13.3 ± 1.7†† | 0.068 | 9.6 ± 1.4 | 10.5 ± 1.2 | 0.161 |
| TBW [L]          | 30.3 ± 4.0** | 32.5 ± 4.0†† | 0.246 | 24.5 ± 3.8 | 25.5 ± 3.2 | 0.526 |
| ECW/TBW [-]      | 0.39146 ± 0.00812 | 0.40909 ± 0.00604 | <0.001 | 0.39240 ± 0.001002 | 0.41052 ± 0.00889 | <0.001 |
| Fat-free mass [kg] | 41.0 ± 5.4** | 43.7 ± 5.3†† | 0.290 | 33.2 ± 5.2 | 34.5 ± 4.3 | 0.575 |
| Fat mass [kg]    | 16.0 ± 4.8  | 9.4 ± 6.1   | 0.05   | 14.1 ± 8.2 | 8.3 ± 4.5 | 0.075 |
| %Fat mass [%]    | 27.7 ± 5.8  | 17.4 ± 9.0  | <0.05  | 28.5 ± 11.4 | 18.8 ± 8.8 | 0.059 |
| %BV [%]          | -14.28 ± 3.04 | -8.42 ± 2.45 | <0.001 | -12.43 ± 3.10 | -6.22 ± 1.90 | <0.001 |
| VI [%(h)/(mL/h/kg)] | -0.32 ± 0.08 | -0.13 ± 0.05 | <0.001 | -0.30 ± 0.06 | -0.14 ± 0.04 | <0.001 |
| S-BP [mmHg] (pre-HD) | 122.3 ± 13.5 | 151.1 ± 11.2 | <0.001 | 118.9 ± 13.3 | 160.3 ± 23.2 | <0.001 |
| D-BP [mmHg] (pre-HD) | 66.4 ± 10.5 | 83.3 ± 18.0 | <0.05 | 65.0 ± 14.4 | 76.6 ± 9.0 | 0.054 |
| S-BP [mmHg] (post-HD) | 123.7 ± 14.9 | 161.1 ± 18.8 | <0.001 | 117.0 ± 25.9 | 167.1 ± 21.6 | <0.001 |
| D-BP [mmHg] (post-HD) | 67.4 ± 8.7 | 76.9 ± 16.1 | 0.164 | 61.3 ± 13.1 | 76.9 ± 11.4 | <0.05 |
| CTR [%] (post-HD) | 46.1 ± 2.7 | 53.2 ± 1.1†† | <0.001 | 48.6 ± 3.2 | 58.3 ± 4.3 | <0.001 |
| BNP [pg/mL] (post-HD) | 233.7 ± 262.3 | 956.4 ± 1095.4 | 0.102 | 139.7 ± 56.8 | 791.5 ± 594.4 | <0.05 |

DW group; male HD patients vs. female HD patients, *p < 0.05, **p < 0.01, and ***p < 0.001
OH group; male HD patients vs. female HD patients, 'p < 0.05, †p < 0.01, and ††p < 0.001
DW: dry weight, OH: overhydration, ExFv: excess fluid volume, BMI: body mass index, ICW: intracellular water, ECW: extracellular water, TBW: total body water, ECW/TBW: ratio of extracellular water to total body water, %BV: percent change of circulating blood volume, VI: volume index, S-BP: systolic blood pressure, D-BP: diastolic blood pressure, CTR: cardiothoracic ratio, BNP: brain natriuretic peptide
measured by MF-BIA [4]. However, they reported that the DW was overestimated by 0.87 kg on average compared with that obtained by clinical evaluation [4]. Additionally, Lopot et al. developed another method for setting the DW by estimating the ultrafiltration volume to fit the relationship between the ECW/TBW and age of HD patients to that of healthy subjects based on the positive correlation between ECW/TBW and age in healthy subjects [5]. In their study, the ECW/TBW of HD patients obtained at the body weight after ultrafiltration, the volume of which was estimated using the method established by Lopot et al., was overestimated by 1.02 ± 6.28% compared with that of healthy subjects, with large deviations [5]. Apparently, in those previous reports, there were large deviations in the differences between the estimated DW based on the body composition of healthy subjects and the clinically evaluated DW. A possible reason for those deviations is that the correlation equations between the ECW and body weight or between the ECW/TBW and age of the healthy subjects adopted as a reference for setting the DW included large variance, which was affected by muscle mass or fat mass, i.e., the obesity level of individual subjects [5, 11, 12]. In addition, because a water content in adipose tissue is reported approximately 10% [13] and causes increased ECW/TBW, it may be difficult to compare the ECW/TBW between “lean” and “obese” subjects with different %fat mass [11]. Therefore, the adequacy of ECW/TBW as an evaluation index for body water distribution remains disputable.

Recently, an estimation method for mass of excess fluid was developed as an evaluation method of body water distribution based on the body composition model of healthy subjects by incorporating the water content of adipose and lean tissues [11]. The MF-BIA device based on this method was reported to accurately estimate ExFv by adding the water content in adipose tissue to the ECW [11], and the clinical usefulness of this method in setting DW of HD patients has been reported previously [14]. However, as each of the commercially available MF-BIA devices uses a different method for estimating body water volume [1], it is necessary to use the same device to estimate ExFv when evaluating the water content of adipose tissue.

In contrast, the ECW–TBW correlation equations presented in the present study were based on the ECW and TBW data obtained from a large number of healthy adults. Therefore, the residual error (ΔECW) of the measured ECW from the ECW–TBW correlation equations (disposition of the ECW–TBW correlation equations) was within a very narrow range, approximately ± 0.2 L. Furthermore, our recent study demonstrated that the reference value of body water distribution can be estimated more accurately by incorporating the relative increase of ECW (increase of ECW/TBW) with aging [6]. As such, in this study, we introduced the age correction into the ECW–TBW correlation equations, which were used as a reference for calculating the ExFv. Therefore, age correction enables more accurate estimation of “ideal” ECW of HD patients [6], which is a reference for estimating ExFv from TBW and age, and may improve the estimation accuracy of ExFv for HD patients.

In addition, because the ECW–TBW correlation equations for healthy adults were less affected by %fat mass and BMI in the subjects from “lean” to “moderate obese” (WHO class I–II) [6], they may be an appropriate reference of the body water distribution of HD patients compared with the correlation between ECW and body weight, which may be affected by body fat [4]. Although the ExFv estimation method introduced in this study needs the MF-BIA-measured ECW–TBW correlation equation of healthy subjects, no other specific device is needed, and the ExFv in HD patients can easily be estimated, unlike that in Chamney et al.’s method, wherein the water content in fat mass must be incorporated [11].

In this study, the ExFv calculated from the age-corrected ECW–TBW correlation equations of the healthy adults were 0.06 ± 0.19 L in the male DW group and 0.06 ± 0.16 L in the female DW group. These small ExFv values indicated that the “ideal” ECW estimated from the ECW–TBW correlation equations of the healthy subjects and the measured ECW of the DW group in HD patients were nearly equal, and the deviations of the differences were negligibly small. In contrast, the ExFv of the OH group were 0.78 ± 0.32 L in males and 0.51 ± 0.18 L in females, indicating a significantly higher ECW than in the healthy subjects by ≥ 0.5 L. Therefore, “ExFv” based on the age-corrected ECW–TBW correlation equations of healthy adults could discriminate more accurately the state of body water distribution of the clinically OH group from that of the DW group in HD patients.

Accordingly, the ExFv estimation equations derived in this study allow simple and quantitative evaluation of the difference in body fluid volume between HD patients and healthy subjects, and may be a clinically useful index of body water distribution that is less affected by body fat.

Limitations

The relatively small number of HD patients satisfying the selection criteria of the clinical DW and OH groups (CTR, blood pressure, and VI) may have affected the statistical analysis results. Additionally, the clinical indices used for the DW group were the conventional evaluation indices for the OH state of HD patients [7, 8, 15], and thus, it may not have been possible to distinguish subjects in an underhydrated state. Accordingly, some underhydrated patients might have been included in the DW group. Further studies are necessary to distinguish HD patients in the appropriate body water state from those in an underhydrated state.
Conclusions

We derived ExFv estimation equations for HD patients with age correction (increasing ECW/TBW with aging) based on the correlation equations between the MF-BIA-measured ECW and TBW in healthy adults, and examined their applicability to clinical settings. The ExFv values obtained from the estimation equation in the clinical OH group were significantly higher than those of the DW group. Therefore, the newly derived ExFv estimation equations may be a clinically useful index that allows simple and quantitative evaluation of the body water distribution of HD patients.

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Conflict of interest The authors declare that they have no conflict of interest related to this study.

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