Monitoring Volume Status Using Bioelectrical Impedance Analysis in Chronic Hemodialysis Patients

Chae Rim Kim, Jung-ho Shin, Jin Ho Hwang, and Su Hyun Kim

Fluid overload can be an independent risk factor of cardiovascular events and all-cause death in end-stage renal disease (ESRD) patients on chronic hemodialysis. We performed a retrospective study to investigate whether intermittent control of fluid status decreases the rate of these complications using bioelectrical impedance analysis (BIA). In ESRD patients on chronic hemodialysis, we identified the ratio of extracellular water to total body water (ECW/TBW) every 6 months using InBody S10 (Biospace, Seoul, Korea), which was measured within 30 minutes after dialysis initiation on the first dialysis day of the week. The uncontrolled group included 57 (40.1%) patients with all ECW/TBW measurements ≥0.40; in contrast, the controlled group included 85 (59.9%) with any measured ECW/TBW <0.40. Included patients were followed for 29 (12-42) months. The risk of cardiovascular events was higher in the uncontrolled group (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.2–5.1; p < 0.05) than it was in the controlled group; however, this difference disappeared after adjusting for age, sex, and Charlson comorbidity index (not significant). On the other hand, the patients in the uncontrolled group had a higher risk of all-cause death than did those in the controlled group, independent of age, sex, and Charlson comorbidity index (HR, 4.7; 95% CI, 1.4-16.1; p < 0.05). In conclusion, monitoring volume status using BIA may help to predict all-cause death in chronic hemodialysis patients. Further controlled studies are needed to confirm that strict volume control could reduce the rates of cardiovascular events and mortality in this population. ASAIO Journal 2017; XX:00-00.

Key Words: fluid overload, bioelectrical impedance analysis, chronic hemodialysis, cardiovascular event, mortality

Volume overload is a critical risk factor for morbidity and mortality in end-stage renal disease (ESRD) patients on chronic hemodialysis (CHD).¹ Fluid retention causes various problems, including hypertension, pulmonary edema, and heart failure.^{2,3} All of these side effects of fluid retention can contribute to cardiovascular and all-cause death.^{2,3} Therefore, maintaining

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Correspondence: Jung-ho Shin, Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, 102, Heukseok-ro, Dongjak-gu, Seoul 06973, Korea. Email: junghoshin1982@gmail.com.

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appropriate volume status (by maintaining an appropriate dry weight) is critical to avoid such complications. Previous studies have found that strict control of dry weight can reduce pulse pressure and blood pressure (BP) by reducing end-diastolic cardiac pressure and limiting ventricular remodeling.^{4,5} Eventually, dry weight maintenance control could help to prevent cardiovascular events and all-cause death.⁶

It is critical to have the ability to precisely measure the volume status to maintain an adequate dry weight. Clinical assessments, including monitoring of BP, body weight, and jugular venous pressure, are frequently used as markers of volume status, but have poor sensitivity.7 Several studies have attempted to characterize more practical and objective techniques to assess volume status.^{8–10} Bioelectrical impedance analysis (BIA) is one promising tool. Bioelectrical impedance analysis quantifies the human body composition. From this measurement, the ratio of extracellular water to total body water (ECW/TBW) can be calculated. The ECW/TBW has been purposed as an index of volume status in hemodialysis patients because excess volume primarily accumulates in the ECW.11 Prior studies have found that volume overload, as assessed by BIA, is associated with high BP and decreased overall survival in ESRD patients on maintenance hemodialysis.^{12,13} However, those studies only analyzed the single BIA results. No prior studies have investigated the impact of chronic volume overload on outcomes using longitudinal BIA data.

This retrospective study analyzed the longitudinal data obtained from BIA in ESRD patients on CHD. We hypothesized that patients whose volume status was controlled, even intermittently, would have better clinical outcomes compared with those whose volume status was persistently overloaded. Thus, we sought to determine the impacts of chronic fluid overload on BP, cardiovascular events, and all-cause mortality by comparing patients with sustained high ECW/TBW to those with intermittently controlled ECW/TBW.

Methods

Patients

Adult ESRD patients who had been on outpatient CHD for at least 3 months were recruited between October 2011 and October 2015. We recruited 147 eligible patients who received CHD for ESRD at our hemodialysis center during the study period. Body composition was assessed in 145 of these patients. Furthermore, three patients were excluded; one did not have baseline laboratory data, whereas two others had follow-up periods <1 month after body composition analysis. Therefore, this study included a total of 142 ESRD patients on CHD. This study was approved by the Institutional Review Board (IRB) of Chung-Ang University Hospital (number: C2016146[1889]). Because the study was retrospective

From the Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea.

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and the subjects were de-identified, the IRB waived the need for written consent from patients.

Data Collection

Demographic and clinical data were collected from the electronic medical records. These included age, sex, height, predialysis and postdialysis body weight, cause of ESRD, duration of renal replacement therapy, and the presence of residual renal function. Body mass index was calculated by dividing the patient's weight in kilograms by the square of their height in meters. The burden of comorbidity was assessed using the modified Charlson comorbidity index.14 The modified index was calculated as follows: 1 point was assigned for history of coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, or diabetes without end-organ damage; 2 points for hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumor without metastases, leukemia, lymphoma, and myeloma; 3 points for moderate or severe liver disease; and 6 points for metastatic solid tumor or acquired immunodeficiency syndrome. Age was not included in the modified Charlson comorbidity index of the current study. Instead, it was used for the adjustment in multivariate analysis.

All blood samples were drawn under fasting conditions before the first-in-week dialysis sessions, except postdialysis blood urea nitrogen (BUN). Laboratory data included hemoglobin, albumin, BUN, intact parathyroid hormone (PTH), and total carbon dioxide (CO₂). Blood pressure was recorded before the start of the first dialysis after a weekend. We recorded the number of antihypertensive drugs. Dialysis adequacy (Kt/V_{urea}) and protein catabolic rate were estimated using a single-pool urea kinetic model.¹⁵ These clinical data were measured every 6 months during the study period.

Body Composition Analysis

Body composition was assessed using a segmental multifrequency BIA device (InBody S10; Biospace, Seoul, South Korea), which measured the body composition of the trunk and each limb separately. Segmental BIA is more appropriate for monitoring body composition during hemodialysis treatment than whole-body BIA.¹⁶ Eight electrodes were placed on the surface of the thumb, fingers of the hand, and ball of the foot and heel; then, impedance was measured at frequencies of 1, 5, 50, 250, 500, and 1,000 kHz in the supine position. Bioelectrical impedance analysis was measured within 30 minutes after initiation of dialysis, and this measurement was conducted on the first dialysis day of the week. All BIA tests were carried out by nursing staff who were trained in the manufacturer's protocol. Measurements were taken every 6 months using the same technique.

Several BIA-derived parameters including ECW, intracellular water, and TBW were obtained. Among the various parameters derived from BIA, we used the ECW/TBW for the estimation of volume status.¹⁷ Volume overload was defined as the ECW/TBW \geq 0.40 based on the manufacturer's suggestion derived from fluid status data from 6,520 normal healthy Koreans (Biospace, Seoul, South Korea). Because this ratio can be

influenced by age, sex, and comorbidities,^{11,18} these variables were used for the adjustment in multivariate analyses.

All physicians at our hemodialysis center collected BIA data including ECW/TBW. However, whether dry weight was adjusted according to ECW/TBW depended on the physician preference. This study sought to determine whether patients who had controlled ECW/TBW would have better outcomes, compared with those with persistently high ECW/TBW. Therefore, the patients were divided into two volume groups according to this ratio. The uncontrolled group included those with all ECW/TBW measurements \geq 0.40, whereas the controlled group included patients with any measured ECW/TBW <0.40 during the study period.

Outcomes

We first evaluated the longitudinal changes in ECW/TBW between the controlled and uncontrolled groups. Next, we investigated the systolic and diastolic BPs in the two groups during the study period. Finally, we sought to determine the impact of chronic volume overload on outcomes such as hospitalization due to cardiovascular events and all-cause death. To do so, we compared the cumulative incidence and calculated the hazard ratio (HR) for events. Cardiovascular events included cardiac death, acute coronary syndrome, cerebrovascular accident, acute exacerbation of heart failure, and acute peripheral artery occlusion.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). These data were compared using the independent t-test or the Wilcoxon rank-sum test. In contrast, categorical variables, expressed as number (%), were analyzed using the Chi-squared test. The cumulative incidence of death and cardiovascular events was estimated using the Kaplan–Meier method and was compared between the groups using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to determine the HR for events. Age, sex, and modified Charlson comorbidity index were adjusted in multivariate analyses. Data analyses were performed using the Statistical Package for the Social Sciences Version 18.0 (IBM Corp., Armonk, NY). The level of significance was set to a two-sided *p* value of <0.05.

Results

Patient Characteristics

A total of 142 CHD patients were included in this study and were followed for a median of 29 (12–42) months. Based on the ECW/TBW values, 85 (59.9%) and 57 (40.1%) patients were classified into the controlled and uncontrolled groups, respectively. Baseline ECW/TBW was 0.39 ± 0.01 in the controlled group and 0.42 ± 0.01 in the uncontrolled group (p < 0.001). **Table 1** shows the baseline characteristics by group. Patients in the uncontrolled group were older and had higher modified Charlson comorbidity indices (p < 0.01 and p < 0.001) than did those in the controlled group. The initial level of serum albumin was significantly lower in the uncontrolled group than it was in the controlled group (p = 0.001). There were no significant differences between the two groups with

Baseline Characteristics	Total (N = 142)	Controlled Group (n = 85)	Uncontrolled Group (n = 57)	р
Male, n (%)	75 (52.8)	50 (58.8)	25 (43.9)	NS
Age (years)	64 ± 13	62 ± 13	68 ± 12	< 0.01
Dialysis duration (months)	22 (5–57)	18 (5–46)	25 (6–68)	NS
Diabetes, n (%)	81 (57.0)	40 (47.1)	41 (71.9)	< 0.01
Charlson comorbidity index	6 (5–7)	6 (5–7)	7 (6–8)	< 0.001
Residual renal function, n (%)	70 (49.3)	48 (56.5)	22 (38.6)	< 0.05
Body mass index, kg/m ²	23.4 ± 8.5	22.9 ± 3.4	24.2±12.8	NS
Interdialytic weight gain, kg	1.8 ± 0.7	1.8 ± 0.8	1.7 ± 0.6	NS
Hemoglobin, g/dl	10.6 ± 1.0	10.7 ± 0.9	10.5 ± 1.2	NS
Albumin, g/dl	3.8 ± 0.3	3.9 ± 0.3	3.7 ± 0.4	0.001
Intact PTH, pg/ml	214 (132–352)	221 (139–355)	214 (120–334)	NS
Total CO ₂ , mmol/L	23.1±3.1	22.7±3.0	23.7±3.0	NS
Kt/V	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	NS
Protein catabolic rate, mg/kg/d	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	NS
ECW, L	13.7 ± 2.7	13.7 ± 2.7	13.5 ± 2.6	NS
TBW, L	34.1 ± 6.7	35.1±7.1	32.6 ± 6.0	< 0.05
ECW/TBW	0.40 ± 0.01	0.39 ± 0.01	0.42 ± 0.01	< 0.001

Table 1. Baseline Characteristics According to Volume Status in Chronic Hemodialysis Patients

Continuous variables are expressed as mean value ± standard deviation or median (interquartile range), and categorical variables are expressed as n (%).

CO,, carbon dioxide; ECW, extracellular water; NS, not significant; PTH, parathyroid hormone; TBW, total body water.

respect to the levels of hemoglobin, intact PTH, total CO₂, Kt/ $V_{urea'}$ and protein catabolic rate.

Changes in Volume Status

We performed BIA every 6 months during the study period. A total of 643 ECW/TBW values were measured. To identify any trends between volume status and the controlled and uncontrolled groups, the mean ECW/TBW was compared for 36 months (**Figure 1**). The significant differences between the two groups with regard to ECW/TBW persisted from baseline to 36 months (all p < 0.001).

Blood Pressure and Antihypertensive Medications

We compared the BP measurements between the two groups every 6 months for 24 months (Figure 2). The baseline

systolic BP was 148 ± 21 mm Hg in the controlled group and 157 ± 22 mm Hg in the uncontrolled group (p < 0.01). The overall systolic BP measurements were higher in the uncontrolled group than in the controlled group. However, there were only significant differences in BP in months 0, 6, and 12 (all p < 0.01, respectively, **Figure 2A**). In contrast, diastolic BP did not differ between the groups, except for those at 6 and 18 months (p < 0.01 and 0.05, respectively, **Figure 2B**).

We also evaluated the number of antihypertensive medications prescribed in both groups. The initial number of drugs was 2 (1–2) in the controlled group and 2 (1–3) in the uncontrolled group (not significant [NS]). The subsequent numbers of medications were slightly higher in the uncontrolled group than in the controlled group (1 [0–2] and 1 [0–2] at 6 and 12 months in the controlled group *vs.* 2 [1–3] and 2 [1–3] at 6 and 12 months in the uncontrolled group, respectively; both NS).



Figure 1. The comparison of volume status over time according to volume group. Volume status, as expressed by ECW/TBW, was compared between the two groups. The baseline ECW/TBW was 0.39 in the controlled group and 0.42 in the uncontrolled group (p < 0.001). This significant difference between the groups persisted throughout the study period (all p < 0.001). ***p < 0.001. ECW, extracellular water; TBW, total body water.



Figure 2. The comparison of BP according to volume group. **A**: Systolic BP was compared during the study period. The overall systolic BP measurements were higher in the uncontrolled group than they were in the controlled group. The statistical differences were seen in months 0, 6, and 12, but not in month 18 or 24 (p < 0.01, p < 0.01, and p = 0.001; NS and NS, respectively). **B**: Changes in diastolic BP were also compared between the two groups. In contrast to systolic BP, diastolic BP did not show a trend. The diastolic BP differed in months 6 and 18 between the two groups (NS, p < 0.01; NS, p < 0.05; and NS in 0, 6, 12, 18, and 24 months, respectively). *p < 0.05, **p < 0.01, and ***p < 0.001. BP, blood pressure; NS, not significant.

Clinical Outcomes According to Volume Status

Cardiovascular events occurred in 13 patients in the controlled group and in 15 in the uncontrolled group. The 3-year rate of events was 18.3% and 33.9%, respectively (p < 0.05). However, this association was not present in multivariate analysis after adjusting for age, sex, and modified Charlson comorbidity index (HR, 1.7; 95% confidence interval [CI], 0.8–3.7; NS; **Table 2** and **Figure 3A**).

Four patients in the controlled group and 11 in the uncontrolled group died during the study period. The 3-year mortality rate was 4.9% and 23.8% in the controlled and uncontrolled groups, respectively (p = 0.001). Univariate analysis demonstrated that chronic, uncontrolled fluid retention was associated with allcause death. This association persisted in multivariate analysis after adjustment for age, sex, and modified Charlson comorbidity index (HR, 4.7; 95% Cl, 1.4–16.1; p < 0.05; **Table 3** and **Figure 3B**).

Discussion

We used a segmental multifrequency BIA device to investigate the impact of chronic fluid overload in ESRD patients on maintenance hemodialysis. Patients were divided into those with intermittently controlled and uncontrolled volume status, as measured by the ECW/TBW ratio. Although systolic BP differed between the groups, there were no differences in diastolic BP or number of antihypertensive medications. Ultimately, we evaluated the impact of chronic volume overload on cardiovascular events and all-cause mortality in patients with ESRD on CHD. The incidence of cardiovascular events and all-cause mortality was higher in uncontrolled patients than it was in controlled patients. In multivariate analyses (after adjusting for age, sex, and modified Charlson comorbidity index), the association between chronic volume overload and cardiovascular events was no longer observed. In contrast, chronic volume overload was an independent predictor for all-cause mortality in ESRD patients receiving CHD.

Volume overload in CHD patients is a frequent problem.¹⁹ Previous studies have demonstrated that it is associated with arterial hypertension, left ventricular hypertrophy, heart failure, and elevated mortality rate.^{2,3,19} Therefore, it is crucial to make precise assessments of the volume status in this patient population. Unfortunately, there is no single gold-standard method

	Univariate	p	Multivariate*	р
Age	1.0 (1.0–1.1)	< 0.05	1.4 (0.6–3.2)	NS
Sex	1.0 (0.5–2.2)	NS	1.0 (0.5–2.2)	NS
Body mass index	1.0 (0.9–1.0)	NS	(),	
Diabetes	1.9 (0.8–4.3)	NS		
Charlson comorbidity index	1.4 (1.2–1.6)	< 0.001	1.3 (1.1–1.6)	0.001
Residual renal function	0.6 (0.3–1.3)	NS	(),	
Interdialytic weight gain	1.4 (0.8–2.5)	NS		
Albumin	0.4 (0.1–1.1)	NS		
Kt/V	0.7 (0.2–2.5)	NS		
Protein catabolic rate	3.8 (0.8–18.9)	NS		
Uncontrolled group	2.4 (1.2–5.1)	< 0.05	1.7 (0.8–3.7)	NS

Table 2. Impact of Chronic Volume Overload on Cardiovascular Events in Chronic Hemodialysis Patients

*Adjusted for age, sex, and modified Charlson comorbidity index. NS, not significant.

to measure the volume status, although several methods have been considered. Clinical approaches such as measuring peripheral edema are often subjective and do not accurately reflect volume status in CHD patients.²⁰ Other strategies that have been suggested include using the BP, BNP, N-terminal proBNP, or ultrasonic evaluation of the diameter of the inferior vena cava.^{8,9,21,22} However, the relationship between BNP, N-terminal proBNP, and volume status is complex and not entirely clear.^{23,24} In addition, the echocardiographic parameter only assesses a parameter that is related to intravascular volume.²⁵ The BIA, which helps to determine body composition with ECW and TBW, is a useful, objective, and reliable tool to monitor fluid status in patients on dialysis. Its value for assessing volume overload and predicting clinical prognosis has been demonstrated in several prior papers.^{10–13} Similar to this study, Tangvoraphonkchai and Davenport¹² found that high ECW/TBW was associated with increased mortality in hemodialysis patients, although N-terminal proBNP was not. On the other hand, Kim et al.13 used ECW/intracellular water as an integrating marker reflecting both fluid overload and malnutrition, and demonstrated its association with cardiovascular events as well as all-cause mortality. However, most studies have analyzed the single BIA results for predicting future outcomes. We then investigated the impact of chronic volume overload on outcomes using longitudinal BIA data.

We assessed volume status using ECW/TBW, which was a useful predictor of survival in previous studies.^{12,17} This ratio is easy to use and intuitive. The current study used an ECW/TBW of 0.40 as the cut-off value to divide patient volume status, which was based on a fluid status measurement in normal healthy Koreans (suggested by the manufacturer, Biospace, Seoul, South Korea). However, ECW/TBW can be affected by various factors including age, sex, and comorbidities.^{11,18} Accordingly, an ECW/TBW of 0.40 is not an absolute cut-off for defining volume overload. Given this problem, an individualized approach using trends in longitudinal BIA data is reasonable for application in clinical practice until further studies establish an optimal cut-off value for diagnosing volume overload in ESRD patients on CHD.

Several aspects of the techniques used in this study are needed to be noted. Our center measured BIA within 30 minutes after dialysis initiation on the first dialysis day after the weekend. This is not the most accurate way to measure BIA, typically before of 30 minutes after dialysis treatment on a midweek session is recommended.²⁶ The protocol we used took into consideration

work convenience, manpower, and patient compliance. However, BIA was performed at a consistent time by specially trained nursing staff to minimize errors related to measurement. We also used a segmental BIA system, which seems to be more accurate during hemodialysis than whole-body BIA.¹⁶

In this study, patients in the controlled group had lower systolic BP than did those in the uncontrolled group, although no significant difference between the two groups was observed in the later period of the study. Previous studies have demonstrated that fluid overload affects the BP, especially the systolic BP; these changes could increase the morbidity and mortality of ESRD patients.^{4,5} We did not demonstrate whether a decrease in ECW/TBW can reduce BP or the number of required antihypertensive drugs. However, our results might indirectly indicate that a reduction in body weight (to maintain euvolemic status) is a simple and efficacious way to improve BP control in patients on dialysis.^{4,27,28}

This study identified an association between chronic volume overload and cardiovascular disease in univariate analysis; however, this result was not observed in multivariate analysis. Volume overload is known to be associated with long-term cardiovascular complications in hemodialysis patients.^{3,13,29} The negative result in this study could have been influenced by the definition of cardiovascular events. We defined cardiovascular events as the de novo occurrence of cardiac death, acute coronary syndrome, cerebrovascular accident, acute exacerbation of heart failure, or acute peripheral artery occlusion. Chronic fluid retention is mainly associated with the development of heart failure and pulmonary edema.^{2,30,31} The relationships between fluid retention and other cardiovascular diseases, such as atherosclerosis-related disease, are uncertain. However, some reports have shown that fluid retention is associated with atherosclerosisrelated disease.^{3,13,29} These groups explain that fluid overload influences the vascular and endothelial levels and contributes to arterial stiffness, atherosclerosis, and left ventricular hypertrophy.³² Nevertheless, this is only a hypothesis, and further evidence is needed to understand the relationship between volume overload and atherosclerosis-related cardiovascular disease. In addition, multiple factors such as vascular calcification can result in the development of cardiovascular events in patients with chronic kidney disease.³³ An association between fluid overload and atherosclerosis is not supported by our findings.

It is important to note that chronic fluid retention increased the rate of all-cause death in ESRD patients receiving CHD in this study. Furthermore, this impact persisted after adjusting for



Figure 3. The adjusted estimated incidence of cardiovascular events and all-cause death according to volume group. **A**: The rate of cardiovascular events differed in univariate analysis, while it did not after the adjustment for age, sex, and modified Charlson comorbidity index (NS). **B**: The incidence of all-cause death differed between the two groups in both univariate and multivariate analyses (p < 0.05). *p < 0.05. NS, not significant.

age, sex, and modified Charlson comorbidity index. Some studies have also found an association between volume overload assessed by BIA and increased mortality.^{12,13,29,34,35} Compared with previous studies, this study analyzed the long-term BIA data and evaluated the effects of chronic volume overload on clinical outcomes. In addition, we confirmed that chronic volume overload was an independent risk factor for all-cause death. This study has several limitations to be considered. First, it was subject to information bias given its retrospective nature. However, the subjects in this study visited our center 2–3 times per week, and medical information was regularly recorded. This should have minimized missing and incorrect data. In addition, this study was subject to selection bias because it was not a controlled trial. Although we attempted to adjust the

	Univariate	p	Multivariate*	р
Age	1.1 (1.0–1.1)	< 0.01	1.1 (1.0–1.1)	< 0.05
Sex	2.5 (0.8–7.8)	NS	2.8 (0.9–9.1)	NS
Body mass index	0.9 (0.8–1.0)	NS		
Diabetes	2.0 (0.6–6.2)	NS		
Charlson comorbidity index	1.6 (1.3–2.0)	< 0.001	1.7 (1.3–2.2)	< 0.001
Residual renal function	0.4 (0.1–1.1)	NS		
Interdialytic weight gain	1.3 (0.6–3.0)	NS		
Albumin	0.3 (0.1–1.3)	NS		
Kt/V	0.4 (0.1–2.7)	NS		
Protein catabolic rate	0.8 (0.1–9.1)	NS		
Uncontrolled group	5.6 (1.8–17.7)	< 0.01	4.7 (1.4–16.1)	< 0.05

Table 3. Impact of Chronic Volume Overload on All-Cause Death in Chronic Hemodialysis Patients

*Adjusted for age, sex, and modified Charlson comorbidity index. NS, not significant.

baseline differences by including age, sex, and modified Charlson comorbidity index in the multivariate analyses, there may be other confounding variables. Furthermore, it may be difficult to generalize our findings given that our study was small and performed at a single center. To confirm our results, further large, multicenter studies using BIA are needed.

In conclusion, the study evaluated volume status using BIA and investigated the impacts of chronic fluid overload on various outcomes in ESRD patients on CHD. We found that patients with chronic fluid overload had higher systolic BP than did those with intermittently controlled volume status. This study also suggests that chronic volume overload could be a predictor for all-cause death. Therefore, BIA can be a reasonable method to identify patients with abnormal fluid balance and to maintain adequate dry weight. Furthermore, this approach may reduce the rate of mortality in CHD patients. Additional large, prospective trials are needed to demonstrate whether BIA-guided volume management can limit the adverse outcomes in ESRD patients on CHD.

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