The Effect of Strict Volume Control Assessed by Repeated Bioimpedance Spectroscopy on Cardiac Function in Peritoneal Dialysis Patients

Yu Ah Hong1, Hye Eun Yoon1, Bum Soon Choi1, Seok Joon Shin1, Yong-Soo Kim1, So Young Lee2, Sang-Ho Lee3, Su Hyun Kim4, Eun Young Lee5, Sug Kyun Shin6, Young Joo Kwon7, Jeong Ho Kim1, Yoon Kyung Chang1, Suk Young Kim1, Ji Eun Kim7, Shin Young Ahn1, & Gang Jee Ko7*

Adequate fluid management plays an important role in decreasing cardiovascular risk in peritoneal dialysis (PD) patients. We evaluated whether strict volume control monitored by bioimpedance spectroscopy (BIS) affects cardiac function in PD patients. This study is a secondary analysis of a multicentre, prospective, randomized, controlled trial. Fluid overload was assessed by the average overhydration/extracellular water (OH/ECW) at baseline, 6 months and 12 months. Patients were categorized as time-averaged overhydrated (TA-OH/ECW ≥ 15%) or normohydrated (TA-OH/ECW < 15%), and echocardiographic parameters were compared between groups. Among a total of 151 patients, 120 patients exhibited time-averaged normohydration. Time-averaged overhydrated patients had a significantly higher left atrial (LA) diameter and E/e′ ratio and a lower left ventricular (LV) ejection fraction at 12 months than time-averaged normohydrated patients. LA diameter, end-systolic volume and end-diastolic volume were decreased at 12 months compared to baseline in time-averaged normohydrated patients only. TA-OH/ECW was independently associated with ejection fraction at 12 months (β = −0.190; p = 0.010). TA-OH/ECW, but not OH/ECW at 12 months, was an independent risk factor for LV dysfunction (odds ratio 4.020 [95% confidence interval 1.285–12.573]). Overhydration status based on repeated BIS measurements is an independent predictor of LV systolic function in PD patients.

Cardiovascular disease is the leading cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD)1. Fluid overload is directly linked to hypertension, increased arterial stiffness and left ventricular (LV) hypertrophy2,3 and is an independent predictor of cardiovascular risk and mortality in ESRD patients4–7. Therefore, adequate fluid management is a key strategy to decrease cardiovascular risk in peritoneal dialysis (PD) patients. Chronic fluid overload occurs frequently in PD and non-dialysis CKD or haemodialysis (HD). Indeed, the European Body Composition Monitoring (EuroBCM) study demonstrated that more than 50% of PD patients were overhydrated, and severe fluid overload was present in 25.2% of PD patients8.

Bioimpedance spectroscopy (BIS) is a simple and noninvasive technique for measuring body composition and has been proposed as an effective objective method to assess and monitor the volume status8. Few randomized

1Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea. 2Department of Internal Medicine, Eulji University School of Medicine, Seoul, Republic of Korea. 3Department of Internal Medicine, Kyung Hee University Medical School, Seoul, Republic of Korea. 4Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea. 5Department of Internal Medicine. Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea. 6Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea. 7Department of Internal Medicine, Korea University School of Medicine, Seoul, Republic of Korea. *email: lovesba@korea.ac.kr
controlled trials have demonstrated that BIS-guided fluid management leads to LV mass index regression, decreased blood pressure (BP), improved arterial stiffness, and overall increased survival in maintenance HD patients\(^{10,11}\). However, only one randomized controlled trial demonstrated that fluid management guided by BIS significantly decreased BP in PD patients\(^{12}\). Recent randomized controlled studies have revealed that BIS-guided fluid management did not benefit volume control, residual renal function preservation, or cardiovascular parameters in PD patients\(^{13,14}\). Therefore, the usefulness of BIS measurement for the assessment of fluid balance has been inconclusive in PD patients.

The effects of strict volume control on cardiac outcomes and survival in dialysis patients have been reported in many previous studies\(^{15-17}\). However, traditional approaches, such as cardiothoracic ratio, BP, or brain natriuretic peptide, were not sensitive enough to detect subtle changes in fluid status. Most studies that evaluated the association between fluid overload measured by BIS and echocardiographic parameters in CKD patients were cross-sectional analyses\(^{3,18,19}\). Therefore, the effect of overhydration status assessed by BIS measurements on cardiac function over time remains unclear. The aim of this study was to elucidate whether overhydration status assessed by repeated BIS measurements for one year influences cardiac function in non-anuric PD patients.

**Results**

**Study population.** Figure 1 depicts the study design and contains a flowchart of the study participants. In the original randomized controlled trial, a total of 201 participants were enrolled and randomly assigned to the BIS-guided or the control group. In total, 154 PD patients completed the study (Fig. 1). We excluded three patients who had no BIS measurement results for 6 months. Therefore, 151 patients (53.9 \(\pm\) 12.1 years, 54.3% male) were ultimately included in this study. The mean value of time-averaged overhydration/extracellular water (TA-OH/ECW), the average of overhydration/extracellular water (OH/ECW) at baseline, 6 months and 12 months, was 8.7 \(\pm\) 7.9% (Fig. 2). Thirty-one patients (20.5%) were categorized into the time-averaged overhydrated group (TA-OH/ECW \(\geq\) 15%), and 120 (79.5%) patients were categorized into the time-averaged normohydrated group (TA-OH/ECW < 15%).

**Patient characteristics at baseline and 12 months.** Table 1 shows the study population characteristics at baseline and 12 months. The patients in the two groups were similar regarding age, sex, body mass index (BMI), and presence of hypertension. However, there were more patients with diabetes mellitus (DM) and diabetic kidney disease in the time-averaged overhydrated group. Patients with time-averaged overhydration were taking more anti-hypertensive agents and had a higher ratio of dialysate to serum creatinine (D/P creatinine) from the 4-hr peritoneal equilibrium test (PET) compared to individuals with time-averaged normohydration at both baseline and 12 months. PD duration and daily urine output were similar between the groups. Pulse pressure, but not systolic and diastolic BP, was higher in time-averaged overhydrated patients at baseline and 12 months. Patients with time-averaged overhydration had significantly lower serum albumin levels at baseline and 12 months. Haemoglobin was not different between the two groups at baseline but was significantly decreased in time-averaged overhydrated patients at 12 months. Additionally, serum glucose was markedly higher in time-averaged overhydrated patients than normohydrated patients at baseline but was not significantly different between the two groups at 12 months.

Comparisons of echocardiographic parameters between the time-averaged overhydrated group and the normohydrated group at baseline and 12 months are also found in Table 1. At baseline, the time-averaged overhydrated group exhibited a lower c’ velocity and E/A ratio than did the normohydrated group (p = 0.001 and p = 0.047, respectively). LA volume, LV end-systolic diameter (LVESt), LV end-diastolic diameter (LVEDd),
LV mass index, end-systolic volume (ESV) and end-diastolic volume (EDV) were not different between the two groups at either baseline or 12 months. However, the LA diameter and E/e′ ratio were significantly higher (p = 0.036 and p = 0.004, respectively), and the LV ejection fraction (EF) and e′ velocity were lower in overhydrated patients compared to normohydrated patients (p = 0.034 and p = 0.010, respectively) at 12 months.

Differences in BIS parameters between overhydrated and normohydrated patients at baseline and 12 months. Among body composition parameters measured, total body water (TBW), lean tissue mass (LTM) and adipose tissue mass (ATM) were not significantly different between the time-averaged overhydrated group and normohydrated group at either baseline or 12 months (Fig. 3A–C). Baseline extracellular water (ECW) and overhydration (OH) were further increased in the time-averaged overhydrated group compared to the normohydrated group (Fig. 3D,E, p = 0.016 and p < 0.001, respectively). ECW was no longer significantly different between the two groups at 12 months (Fig. 3D, p = 0.06), but OH remained higher in the time-averaged overhydrated group at 12 months (Fig. 3E, p < 0.001, respectively).

Echocardiographic parameters associated with time-averaged relative hydration status. As shown in Table 2, linear regression analyses were performed to identify associations between echocardiographic parameters at 12 months and TA-OH/ECW. LA diameter, LA volume, LVESd, ESV, and EDV at the end of study were all positively associated with TA-OH/ECW (LA diameter: β = 0.338; p < 0.001, LA volume: β = 0.197; p = 0.032, LVESd: β = 0.220; p = 0.007, ESV: β = 0.240; p = 0.004, and EDV: β = 0.207; p = 0.012), and EF and e′ velocity were negatively associated with TA-OH/ECW in the univariable linear regression analysis (EF: β = −0.230; p = 0.004 and e′ velocity: β = −0.215; p = 0.008). Using the multivariable linear regression, TA-OH/ECW was independently negatively associated with only EF (β = −0.190; p = 0.010) after adjusting for age, PD duration, BMI, baseline OH, pulse pressure, haemoglobin, albumin, glucose, D/P creatinine and echocardiographic parameters that displayed statistical significance in the univariable analysis.

Changes in echocardiographic parameters between baseline and 12 months in time-averaged overhydrated and normohydrated patients. Table 3 shows the differences between baseline and 12-month echocardiographic parameters in the time-averaged overhydrated group and the normohydrated group. The LA volume and LV mass index were significantly decreased at 12 months compared to baseline in both the time-averaged overhydrated and normohydrated patients. However, LA diameter, ESV and EDV were significantly decreased in patients with time-averaged normohydration only (p = 0.014, p < 0.001, and p < 0.001, respectively), and the E/A ratio was significantly decreased at 12 months compared to baseline in patients with time-averaged overhydration only (p = 0.034). EF was decreased at 12 months compared to baseline in patients with time-averaged overhydration; however, this difference was not statistically significant.

The effect of time-averaged overhydration status on LV systolic function at 12 months. To evaluate whether strict volume control during the one-year period was associated with LV systolic function at the end of the study, we performed the univariable and multivariable logistic regression analyses for EF at 12 months (Table 4). In the crude model, patients with time-averaged overhydration had an increased risk of LV systolic dysfunction, defined as EF < 55%, compared to patients with time-averaged normohydration as the reference category (odds ratio (OR) 2.863, 95% confidence interval (CI), [1.065–7.699], p = 0.037). In the multivariable analysis, time-averaged overhydration status was a powerful independent predictor of LV systolic dysfunction (OR 4.020, 95% CI [1.285–12.573], p = 0.017) after adjusting for age, sex, presence of DM, cause of ESRD, PD duration, baseline OH, time-averaged D/P creatinine from 4-hr PET, time-averaged pulse pressure, time-averaged
Table 1. The comparison of clinical and laboratory parameters between study groups at baseline and the end of study. *Abbreviation: BMI, body mass index; BP, blood pressure; CGN, chronic glomerulonephritis; DM, diabetes mellitus; D/P Cr, dialysate/peritoneal fluid creatinine ratio; e′, early diastolic mitral annular tissue velocity; E/A, early diastolic mitral inflow velocity/late diastolic mitral inflow velocity; EDV, end-diastolic volume; E/e′, early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity, EF, ejection fraction; ESRD, end-stage renal disease; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVEFs, left ventricular end-systolic diameter; PD, peritoneal dialysis; PET, peritoneal equilibrium test.

| Laboratory findings         | Baseline (n=120) | 12 months (n=31) |
|----------------------------|------------------|------------------|
| Hemoglobin (g/dL)          | 11.1 ± 1.2       | 10.8 ± 1.5       | 0.241 | 11.1 ± 1.6 | 10.3 ± 1.3 | 0.029 |
| Glucose (mg/dL)            | 122.1 ± 56.7     | 159.4 ± 89.7     | 0.034 | 128.1 ± 70.1 | 153.2 ± 77.6 | 0.084 |
| Serum Creatinine (mg/dL)   | 8.1 ± 2.7        | 7.5 ± 3.1        | 0.289 | 9.5 ± 3.4  | 9.1 ± 3.3  | 0.471 |
| Serum Albumin (g/dL)       | 3.7 ± 0.4        | 3.3 ± 0.5        | <0.001| 3.7 ± 0.4  | 3.4 ± 0.5  | <0.001|
| Echocardiographic parameters|                  |                  |       |            |            |       |
| LA diameter (mm)           | 38.2 ± 6.2       | 40.8 ± 7.2       | 0.052 | 36.7 ± 6.1 | 39.4 ± 6.7 | 0.036 |
| LA volume (ml)             | 48.3 ± 20.8      | 51.5 ± 19.4      | 0.628 | 45.8 ± 22.9 | 49.4 ± 22.4 | 0.477 |
| LVEsd (mm)                 | 32.9 ± 9.7       | 34.1 ± 6.9       | 0.512 | 31.6 ± 10.6 | 34.5 ± 9.4  | 0.165 |
| LVEDd (mm)                 | 50.2 ± 11.1      | 51.1 ± 9.5       | 0.676 | 48.7 ± 11.4 | 50.7 ± 8.5  | 0.359 |
| LV mass index (g/m²)       | 128.6 ± 69.9     | 140.4 ± 61.9     | 0.395 | 121.1 ± 56.1 | 120.1 ± 46.9 | 0.926 |
| ESV (ml)                   | 38.5 ± 21.7      | 39.0 ± 18.6      | 0.904 | 32.2 ± 15.1 | 37.5 ± 18.6 | 0.107 |
| E/DV (ml)                  | 101.8 ± 41.0     | 100.7 ± 35.8     | 0.885 | 83.9 ± 31.7 | 93.7 ± 34.7 | 0.145 |
| EF (%)                     | 62.8 ± 10.1      | 60.0 ± 7.8       | 0.155 | 61.6 ± 6.0  | 58.8 ± 7.9  | 0.034 |
| e′ velocity (cm/sec)       | 5.7 ± 2.8        | 3.7 ± 2.9        | 0.001 | 5.9 ± 4.7   | 3.7 ± 2.6   | 0.010 |
| E/A                        | 0.88 ± 0.44      | 0.77 ± 0.22      | 0.047 | 0.88 ± 0.2  | 0.67 ± 0.14 | 0.347 |
| E/e′                       | 11.7 ± 11.1      | 14.9 ± 6.0       | 0.131 | 10.3 ± 4.4  | 13.3 ± 5.0  | 0.004 |

Table 1. The comparison of clinical and laboratory parameters between study groups at baseline and the end of study. *Abbreviation: BMI, body mass index; BP, blood pressure; CGN, chronic glomerulonephritis; DM, diabetes mellitus; D/P Cr, dialysate/peritoneal fluid creatinine ratio; e′, early diastolic mitral annular tissue velocity; E/A, early diastolic mitral inflow velocity/late diastolic mitral inflow velocity; EDV, end-diastolic volume; E/e′, early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity, EF, ejection fraction; ESRD, end-stage renal disease; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVEFs, left ventricular end-systolic diameter; PD, peritoneal dialysis; PET, peritoneal equilibrium test.

Discussion
In this study, we demonstrated that time-averaged overhydrated PD patients, as assessed by repeated BIS measurements, had a higher LA diameter and E/e′ ratio and a lower EF than did time-averaged normohydrated PD patients at 12 months, and the time-averaged normohydrated status improved the volume-associated echocardiographic parameters after 12 months. Furthermore, time-averaged overhydration was significantly associated with decreased EF in regression analysis, even after adjusting for confounding variables. These findings suggest that hydration status assessed by repeated BIS measurements may be useful to maintain LV systolic function in PD patients.
Various previous studies have reported that fluid overload assessed by BIS is an independent risk factor for all-cause and cardiovascular mortality in dialysis patients. Our original randomized controlled study investigated the clinical benefit of BIS-guided fluid management, targeting OH within ±2 L of the normal range, over conventional management for one year. However, we did not demonstrate differences in clinical outcomes, such as residual renal function, 24-hr urine volume and echocardiographic parameters, between the control and BIS-guided groups. The recently published COMPASS study also did not demonstrate any differences in clinical outcomes between the BIS-guided group and the control group. There are several reasons for the unexpected results regarding the effect of BIS-guided fluid management in these studies. First, the enrolled PD patients all had well-preserved residual kidney function and relatively stable fluid status over the one-year period, even in the control group. Second, although the BIS information was not provided to the physicians, the enrolled patients in the control group had been assessed and managed fluid balance carefully, similar to those in the BIS-guided group, during the study period. Third, the study duration was relatively short and may not have been long enough to demonstrate the benefits of BIS-guided fluid management. These studies indicate that the careful assessment and treatment of fluid status per se is very important, regardless of BIS method use, in PD patients. Therefore, we focused on whether repeated monitoring of volume status using a BIS device had clinical benefits, particularly improved cardiac parameters, in PD patients.

**Figure 3.** The comparison of changes of BIS Parameters between patients with TA-OH/ECW ≥ 15% and TA-OH/ECW < 15% at baseline and the end of study. (A) Total body water, (B) Lean tissue mass, (C) Adipose tissue mass, (D) Extracellular water (ECW), and (E) Overhydration (OH).
at baseline and 12 months, strongly predicted the risk of death and transfer to HD in prevalent PD patients

| Parameter                         | Baseline | 12 months | p value | Baseline | 12 months | p value |
|-----------------------------------|----------|-----------|---------|----------|-----------|---------|
| 12-month LA diameter (mm)         | 38.2 ± 6.2 | 36.7 ± 6.1 | 0.014   | 40.8 ± 7.2 | 39.4 ± 6.7 | 0.305   |
| 12-month LA volume (ml)           | 48.3 ± 20.8 | 45.8 ± 22.9 | <0.001 | 51.5 ± 19.4 | 49.4 ± 22.4 | 0.001 |
| 12-month LVEF (mm)                | 32.9 ± 9.7  | 31.6 ± 10.6 | 0.176   | 34.1 ± 6.9  | 34.5 ± 9.4  | 0.811   |
| 12-month EDV (ml)                 | 50.2 ± 11.1 | 48.7 ± 11.4 | 0.178   | 51.1 ± 9.5  | 50.7 ± 8.5  | 0.837   |
| 12-month LV mass index (g/m²)     | 128.6 ± 69.9 | 121.1 ± 56.1 | 0.046   | 140.4 ± 61.9 | 120.1 ± 46.9 | 0.008 |
| 12-month E/A                      | 38.5 ± 21.7 | 32.2 ± 15.1 | <0.001 | 39.0 ± 18.6 | 37.5 ± 18.6 | 0.488 |
| 12-month EF (%)                   | 101.8 ± 41.0 | 83.9 ± 31.7 | <0.001 | 100.7 ± 35.8 | 93.7 ± 34.7 | 0.148 |
| 12-month LVEF/EF                  | 62.8 ± 10.1 | 61.6 ± 6.0  | 0.147   | 60.0 ± 7.8  | 58.8 ± 7.9  | 0.531   |
| 12-month E/A                      | 5.7 ± 2.8   | 5.9 ± 4.7   | 0.465   | 3.7 ± 2.9   | 3.7 ± 2.6   | 0.615   |
| 12-month LVEF/EF                  | 0.88 ± 0.44 | 0.88 ± 1.2  | 0.857   | 0.77 ± 0.22 | 0.67 ± 0.14 | 0.034   |
| 12-month LVEF/EF/EF               | 11.7 ± 11.1 | 10.3 ± 4.4  | 0.188   | 14.9 ± 6.0  | 13.3 ± 5.0  | 0.144   |

Table 2. Univariable and multivariable linear regressions for time-averaged relative hydration status and echocardiographic parameters at the end of study. *Abbreviation: EDV, end-diastolic volume; E/A, early diastolic mitral inflow velocity/late diastolic mitral inflow velocity; EF, ejection fraction; EPC, end-diastolic volume; LA, left atrial; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular end-systolic diameter; TA-OH/ECW, time-averaged overhydration/extracellular water. The variables included in the multivariable linear regression model were age, PD duration, BMI, baseline OH, time-averaged pulse pressure, time-averaged hemoglobin, time-averaged albumin, time-averaged glucose, time-averaged D/P Creatinine at 4-hr PET and statistically significant variables among echocardiographic parameters in the univariable linear regression (p < 0.1). Dashes indicate that the variable did not enter the multivariable linear regression model.

Table 3. The differences of echocardiographic parameters between baseline and the end of study in time-averaged overhydrated and normohydrated patients. *Abbreviation: e′, early diastolic mitral annular tissue velocity; E/A, early diastolic mitral inflow velocity/late diastolic mitral inflow velocity; EDV, end-diastolic volume; E/e′, early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity; EF, ejection fraction; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular end-systolic diameter.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.

We used the OH/ECW ratio instead of OH to define hydration status in consideration of the body size of the patients, and overhydration status was commonly defined as OH/ECW > 15%.
Strict volume control through moderate salt restriction and diuretic use significantly improved the LV mass at 12 months compared to baseline in the time-averaged normohydrated group and in the overhydrated group. In contrast, the LV mass index was significantly decreased and normohydrated groups at baseline or 12 months. The LV mass index was not significantly different between the time-averaged overhydrated and normohydrated groups at baseline or 12 months. Therefore, more specific research for the relationship between fluid overload and the LV mass index in PD patients may be required.

Our study had some limitations. First, this observational study included both incident and prevalent PD patients, and 70% of the enrolled patients were within one year of initiating PD. We cannot exclude residual confounding factors given the observational study design. Second, the number of patients was relatively small, and the study period was relatively short. Third, despite the multicentre nature of this study, the participants were all Korean PD patients. Therefore, these results may not be applicable to other PD populations. Fourth, EF measured by conventional echocardiography has been shown to be rather insensitive to the detection of LV systolic dysfunction because of intra- and inter-observer variability. Furthermore, LV hypertrophy and changes in LV structure in CKD patients could lead to LV systolic dysfunction despite normal EF. In this respect, LV global longitudinal strain (GLS), the negative ratio of the maximal change in LV longitudinal length in systole to the original length as assessed by speckle tracking echocardiography, is effective in the early detection of LV systolic dysfunction in CKD patients with preserved EF. A recent cross-sectional study showed that fluid overload measured by BIS was negatively correlated with GLS in pre-dialysis CKD patients. Therefore, further studies are needed.

which can result from reduced oncotic pressure due to the significant peritoneal protein losses and decreases in serum albumin in PD patients. Hydration status can also be affected by the rate of solute transfer across the peritoneal membrane. Rapid peritoneal solute transport, namely, high D/P creatinine, is associated with increased protein loss and excess dialysate reabsorption, leading to ultrafiltration problems and overhydration. In addition, pulse pressure, known as arterial compliance, is independently associated with rapid peritoneal solute transport, increased cardiovascular hospitalization, and increased mortality in PD patients. Taken together, these complex clinical factors may contribute to fluid overload in PD patients.

The noteworthy finding of this study is to demonstrate the importance of continuous strict volume control on cardiac function and the usefulness of repeated BIS measurement for monitoring fluid status in PD patients. We found that the time-averaged normohydrated group monitored by repeated BIS measurements had a significantly low LA diameter and E/e’ ratio at 12 months compared to those of the time-averaged overhydrated group and decreased volume-associated echocardiographic parameters, such as LA diameter, ESV and EDV, were observed after 12 months. Fluid overload can lead to increased cardiac workload, increased LV mass, and systolic and diastolic dysfunction caused by myocardial fibrosis. To date, EF is the most frequently used parameter to define LV systolic function and an important prognostic marker of patients with cardiovascular diseases. In the present study, the mean EF value at baseline was not significantly different between the two groups, but EF in patients with time-averaged overhydration was significantly lower than that in patients with time-averaged normohydratation at 12 months. In addition, TA-OH/ECW was significantly associated with EF and an independent predictor of LV systolic dysfunction at 12 months, whereas 12-month OH/ECW did not show an association with LV systolic dysfunction. Although the absolute differences of EF were small between the two groups and the mean EF value even in the overhydrated group was within normal ranges, the association between time-averaged fluid overload measured by BIS and the decrease in LV systolic function was observed in this study.

Several cross-sectional studies have reported that the LV mass index is positively correlated with fluid overload in HD patients. However, we did not confirm the association between TA-OH/ECW and the LV mass index in this study. The LV mass index was not significantly different between the time-averaged overhydrated and normohydrated groups at baseline or 12 months. In contrast, the LV mass index was significantly decreased at 12 months compared to baseline in the time-averaged normohydrated group and in the overhydrated group. This discrepancy may be due to differences in study design, study length, and the definition of overhydration. Strict volume control through moderate salt restriction and diuretic use significantly improved the LV mass index after 3 years in PD patients and one year in HD patients. These two previous studies were retrospective single-arm observation studies that did not compare the LV mass index between overhydrated and normohydrated patients. Therefore, more specific research for the relationship between fluid overload and the LV mass index in PD patients may be required.

Table 4. Univariable and multivariable logistic regression for the predictors of left ventricular systolic dysfunction at the end of study. *Abbreviation: CI, confidence interval; OH/ECW, overhydration/extracellular water; OR, odds ratio; TA-OH/ECW, time-averaged overhydration/extracellular water. Multivariable logistic regression for 12-month OH/ECW was adjusted for Model 1: age, sex, BMI, presence of DM, cause of ESRD, PD duration, baseline OH, 12-month pulse pressure, 12-month D/P creatinine at 4-hr PET, 12-month hemoglobin, 12-month glucose, 12-month albumin, and Model 2: model 1 + 12-month LA diameter, 12-month LV mass index, and 12-month E/e’ ratio. Multivariable logistic regression for time-averaged OH/ECW was adjusted for Model 1: age, sex, BMI, presence of DM, cause of ESRD, PD duration, baseline OH, time-averaged pulse pressure, time-averaged D/P creatinine at 4-hr PET, time-averaged hemoglobin, time-averaged glucose, time-averaged albumin, and Model 2: model 1 + 12-month LA diameter, 12-month LV mass index, and 12-month E/e’ ratio.

|        | Crude OR (95% CI) | Model 1 OR (95% CI) | p value | Model 2 OR (95% CI) | p value |
|--------|------------------|---------------------|---------|---------------------|---------|
| <15%   | 1 (Reference)    | 1 (Reference)       | 1 (Reference) | 1 (Reference)       | 0.994   |
| ≥15%   | 1.646 (0.582–4.654) | 0.347 | 0.736 (0.173–3.119) | 0.667 | 1.006 (0.213–4.738) | 0.994 |
| TA-OH/ECW | <15%  | 1 (Reference)    | 1 (Reference)       | 1 (Reference)       | 0.037   |
| ≥15%   | 2.863 (1.065–7.699) | 0.037 | 4.556 (1.520–13.657) | 0.007 | 4.020 (1.285–12.573) | 0.017 |

Table 4. Univariable and multivariable logistic regression for the predictors of left ventricular systolic dysfunction at the end of study. *Abbreviation: CI, confidence interval; OH/ECW, overhydration/extracellular water; OR, odds ratio; TA-OH/ECW, time-averaged overhydration/extracellular water. Multivariable logistic regression for 12-month OH/ECW was adjusted for Model 1: age, sex, BMI, presence of DM, cause of ESRD, PD duration, baseline OH, 12-month pulse pressure, 12-month D/P creatinine at 4-hr PET, 12-month hemoglobin, 12-month glucose, 12-month albumin, and Model 2: model 1 + 12-month LA diameter, 12-month LV mass index, and 12-month E/e’ ratio. Multivariable logistic regression for time-averaged OH/ECW was adjusted for Model 1: age, sex, BMI, presence of DM, cause of ESRD, PD duration, baseline OH, time-averaged pulse pressure, time-averaged D/P creatinine at 4-hr PET, time-averaged hemoglobin, time-averaged glucose, time-averaged albumin, and Model 2: model 1 + 12-month LA diameter, 12-month LV mass index, and 12-month E/e’ ratio.
using two-dimensional speckle tracking echocardiography may be needed to accurately elucidate the association between fluid overload and LV systolic dysfunction in dialysis patients. Despite these limitations, our study clearly demonstrates the clinical significance of regular BIS measurement for improving echocardiographic parameters in non-anuric PD patients.

In conclusion, strict volume control based on repeated measurements of BIS was an independent predictor of LV systolic function in non-anuric PD patients. Close monitoring by repeated BIS measurement and management to control volume could reduce overhydration-related morbidity and mortality. Further studies are needed to confirm whether adequate fluid management via repeated BIS measurements will lead to improved cardiovascular outcomes in PD patients with overhydration.

Materials and Methods

Study population and design. This study is a secondary analysis of a multicentre, prospective, randomized, controlled trial that was conducted for one year in Korea. Incident or prevalent PD patients from eight tertiary hospitals who were > 18 years old, had been treated for PD for at least three months and who had a daily urine output > 500 mL were enrolled. Patients who were not suitable for BIS measurements due to artificial devices or health conditions were excluded. This study was conducted according to the Declaration of Helsinki. The research protocol was approved by the Institutional Review Board of the Catholic University of Korea, Seoul St. Mary's Hospital, the Institutional Review Board of the Catholic University of Korea, Incheon St. Mary's Hospital, the Institutional Review Board of Eulji University School of Medicine, the Institutional Review Board of Kyung Hee University Medical School, the Institutional Review Board of Chung-Ang University College of Medicine, the Institutional Review Board of Soonchunhyang University Cheonan Hospital, and the Institutional Review Board of National Health Insurance Service Ilsan Hospital and the Institutional Review Board of Korea University School of Medicine, and informed consent was obtained from all participants.

The original study design included the comparison of clinical outcomes between patients with BIS-guided fluid management and those who managed the volume status by physical examinations and clinical assessment depending on symptoms and changes in body weight or BP. The patients were randomly allocated 1:1 to either the BIS or control group. In the control group, fluid was managed on the basis of physical examinations and clinical assessment. BIS measurements were also performed in the control group at baseline, 6 months and 12 months, but clinicians and participants were blinded to the results during the study period. The participants in the BIS group underwent monthly BIS-guided fluid management until OH reached within ± 2 L of normal range, and then BIS was performed every three months. All BIS results were provided to the clinicians and the participants. The prescriptions changed based on the BIS measurements to meet a target OH within ± 2 L of range.

The strategies of fluid management according to the results of BIS measurement or clinical assessment were as below: If patients were regarded in overhydrated status, the clinicians prescribed one or multiple following methods for fluid management as their judgment: (1) the restriction of dietary sodium intake, (2) the increase of diuretic dose or the use of other diuretic, and/or (3) the use of dialysate with higher glucose concentration. If patients were regarded in volume-depleted status, following either one or both were prescribed: (1) the reduction of diuretic dose or the discontinuation of diuretics and/or (2) the decrease of dialysate glucose concentration or the liberal intake of dietary sodium if the patient already underwent PD using the lowest dialysate glucose concentration. If patients were regarded in euvolemic status, the previous fluid management strategy was maintained. The prescriptions for fluid management were chosen based on the clinician's judgment, and multiple prescriptions were permitted.

In this study, we defined the average of OH/ECW at baseline, 6 months and 12 months as the TA-OH/ECW. Patients were categorized into two groups based on relative hydration status during the one-year study period: time-averaged normohydrated and overhydrated groups. We compared changes in echocardiographic parameters from baseline to 12 months between the time-averaged overhydrated and normohydrated groups.

Bioimpedance parameters. The Body Composition Monitor method (BCM, Fresenius Medical Care, Germany) was performed by trained practitioners at each centre. The BIS uses alternating electric currents at 50 frequencies between 5 and 1000 kHz. Measurement of BIS was performed by placing electrodes on one hand and one foot and entering the information of current height and body weight data into the device. Because BIS does not measure sequestered fluid in the trunk, indwelling intra-abdominal dialysate fluid does not influence and one foot and entering the information of current height and body weight data into the device. Because BIS does not measure sequestered fluid in the trunk, indwelling intra-abdominal dialysate fluid does not influence the readings of hydration status. Therefore, participants performed BIS under a dwelling state of dialysate. TBW, LTM, ATM, ECW and OH were identified by the measured BIS data. The OH is the difference between the expected ECW under normal physiological conditions and the actual ECW. Because specific OH values vary in clinical relevance according to the body size of the patient, the OH/ECW ratio reflects relative the hydration status and can be a more accurate indicator of fluid overload than OH alone.

Echocardiographic parameters. All patients underwent echocardiographic evaluation at baseline and the end of the study. A two-dimensional guided M-mode echocardiography was performed by cardiologists at each centre who did not know the clinical and laboratory information for the patient. LVESeD or LVEDDe were measured in the M-mode LV dimension with the short axis view at end-systole and end-diastole. LV mass was calculated using the Devereux formula and the LV mass index was determined from the LV mass/body surface area (g/m²). EF, E, SV, EDV, LA diameter and LA volume were determined from apical two- and four-chamber views by Simpson’s biplane formula. Mitral inflow velocities and LV myocardial tissue velocities were determined using pulsed-wave Doppler and tissue Doppler imaging. We measured the peak early diastolic mitral inflow velocity (E), peak late diastolic mitral inflow velocity (A), and early diastolic mitral annular tissue velocity (e'). The ratio of peak early diastolic mitral inflow velocity to peak early diastolic mitral annular tissue velocity (E/e') and the ratio of peak early diastolic mitral inflow velocity to peak late diastolic mitral inflow velocity (E/A) were calculated.
Clinical and laboratory parameters. Physical examinations were performed at monthly visits. BP was determined as the average of two measurements every five minutes using a single calibrated BP device at each centre. BMI was defined as the formula of body weight/height² (kg/m²). The presence of DM and hypertension, the cause of ESRD, and PD duration were collected from medical records. Peritoneal membrane characteristics were determined by the 4-hr PET, and a D/P creatinine was calculated from the results of the 4-hr PET. Laboratory values and 24-hr urine volume were also collected, and the values at baseline, 6 months and 12 months were averaged to determine the time-averaged values for variables.

Statistical analysis. All parameters were described as the mean ± standard deviation for continuous variables and the percentage for categorical variables. Continuous data were compared using Student’s t-test to detect differences between two groups, and the chi-squared test or Fisher’s exact test was used for categorical variables. Univariable and multivariable linear regression analyses were used to determine the associations between TA-OH/ECW and echocardiographic parameters. The change in echocardiographic parameters from baseline to 12 months was assessed using a paired t-test. Univariable and multivariable binary logistic regression analyses were used to identify whether overhydration status had an influence on decreased EF at the end of study. A value of p < 0.05 was considered statistically significant. All analyses were performed using SPSS Statistics 21.0 (IBM Corporation, Armonk, NY, USA).

Received: 13 March 2019; Accepted: 31 October 2019; Published online: 27 November 2019

References
1. Foley, R. N. & Parfrey, P. S. Cardiovascular disease and mortality in ESRD. *J. Nephrol.* **11**, 239–245 (1998).
2. Kocyigit, I. et al. The association between arterial stiffness and fluid status in peritoneal dialysis patients. *Perit. Dial. Int.* **34**, 781–790, https://doi.org/10.3747/pdi.2013.00057 (2014).
3. Inal, S. et al. Association between bioimpedance analysis parameters and left ventricular hypertrophy in peritoneal dialysis patients. *Int. Urol. Nephrol.* **46**, 1851–1856, https://doi.org/10.1007/s11255-014-0709-y (2014).
4. Kalantar-Zadeh, K. et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* **119**, 671–679, https://doi.org/10.1161/circulationaha.108.807762 (2009).
5. Kim, Y. J. et al. Overhydration measured by bioimpedance analysis and the survival of patients on maintenance hemodialysis: a single-center study. *Kidney Res. Clin. Pract.* **34**, 212–218, https://doi.org/10.1016/j.krcp.2015.10.006 (2015).
6. Wizemann, V. et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol. Dial. Transplant.* **24**, 1574–1579, https://doi.org/10.1093/ndt/gfn707 (2009).
7. Hwang, S. D. et al. Risk of overhydration and lean body mass index as measured using a body composition monitor in patients on hemodialysis: a systematic review and meta-analysis. *Ren. Fail.* **40**, 51–59, https://doi.org/10.1080/0886022x.2017.1419963 (2018).
8. van Biesen, W. et al. A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. *Nephrol. Dial. Transplant.* **28**, 2620–2628, https://doi.org/10.1093/ndt/gft296 (2013).
9. Machek, P., Jirka, T., Moissl, U., Chamney, P. & Wab, P. Guided optimization of fluid status in hemodialysis patients. *Nephrol. Dial. Transplant.* **25**, 538–544, https://doi.org/10.1093/ndt/gft296 (2010).
10. Hur, E. et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. *Am. J. Kidney Dis.* **61**, 957–965, https://doi.org/10.1053/j.ajkd.2012.12.017 (2013).
11. Onofriescu, M. et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am. J. Kidney Dis.* **64**, 111–118, https://doi.org/10.1053/j.ajkd.2014.01.420 (2014).
12. Luo, Y. J., Lu, X. H., Woods, F. & Wang, T. Volume control in peritoneal dialysis patients guided by bioimpedance spectroscopy assessment. *Blood Purif.* **31**, 296–302, https://doi.org/10.1159/000322617 (2011).
13. Oh, K. H. et al. Does Routine Bioimpedance-Guided Fluid Management Provide Additional Benefit to Non-Anuric Peritoneal Dialysis Patients? Results from COMPASS Clinical Trial. *Perit. Dial. Int.* **38**, 131–138, https://doi.org/10.3747/pdi.2016.00241 (2018).
14. Tan, B. K. et al. Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. *Kidney Int.* **89**, 487–497, https://doi.org/10.1038/ki.2015.294 (2016).
15. Ozkayhaz, M. et al. Impact of volume control on left ventricular hypertrophy in dialysis patients. *Nephrol. Ther.* **12**, 94–97, https://doi.org/10.1681/nptd.2015.08.003 (2016).
16. Lin, Y. P. et al. Left ventricular mass and hemodynamic overload in normotensive hemodialysis patients. *Kidney Int.* **62**, 1828–1838, https://doi.org/10.1046/j.1523-7352.2002.00610.x (2002).
17. David, S. et al. Diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for left ventricular dysfunction in patients with chronic kidney disease stage 5 on haemodialysis. *Nephrol. Dial. Transplant.* **23**, 1370–1377, https://doi.org/10.1093/ndt/gfn700 (2008).
18. Li, J. et al. Short Body Height and Pre-pregnancy Overweight for Increased Risk of Gestational Diabetes Mellitus: A Population-Based Cohort Study. *Frontiers in endocrinology* **3**, 239, https://doi.org/10.3389/fendo.2018.00349 (2018).
19. Yilmaz, A., Yilmaz, B., Kucukseymen, S., Orepel, E. & Pekel, N. Association of overhydration and cardiac dysfunction in patients have chronic kidney disease but not yet dialysis. *Nephrol. Ther.* **12**, 94–97, https://doi.org/10.1681/nptd.2015.08.003 (2016).
20. O’Lone, E. L., Visser, A., Finney, H. & Fan, S. L. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. *Nephrol. Dial. Transplant.* **29**, 1430–1437, https://doi.org/10.1093/ndt/gfu049 (2014).
21. Onofriescu, M. et al. Overhydration, Cardiac Function and Survival in Hemodialysis Patients. *PLoS One* **10**, e0135691, https://doi.org/10.1371/journal.pone.0135691 (2015).
22. Zoccali, C. et al. Chronic Fluid Overload and Mortality in ESRD. *J. Am. Soc. Nephrol.* **28**, 2491–2497, https://doi.org/10.1681/asn.2016121341 (2017).
23. Yoon, H. E. et al. Bioimpedance spectroscopy-guided fluid management in peritoneal dialysis patients with residual kidney function: A randomized controlled trial. *Nephrology (Carlton)*, https://doi.org/10.1111/nph.13571 (2019).
24. Wabel, P. et al. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrol. Dial. Transplant.* **23**, 2965–2971, https://doi.org/10.1093/ndt/gfn228 (2008).
25. Kim, J. K., Song, Y. R., Lee, H. S., Kim, H. J. & Kim, S. G. Repeated Bioimpedance Measurements Predict Prognosis of Peritoneal Dialysis Patients. *Am. J. Nephrol.* **47**, 120–129, https://doi.org/10.1159/000486801 (2018).
26. Jones, C. H., Smye, S. W., Newstead, C. G., Will, E. J. & Davison, A. M. Measurement of extracellular fluid volume determined by bioelectric impedance and serum albumin in CAPD patients. *Nephrol. Dial. Transplant.* **13**, 393–397 (1998).
27. Dümler, F. Hypoalbuminemia is a marker of overhydration in chronic maintenance patients on dialysis. *ASAIO J.* **49**, 282–286 (2003).
28. Plum, J. et al. Comparison of body fluid distribution between chronic haemodialysis and peritoneal dialysis patients as assessed by biophysical and biochemical methods. *Nephrol. Dial. Transplant.* **16**, 2378–2385 (2001).
29. Konings, C. J. et al. Fluid status in CAPD patients is related to peritoneal transport and residual renal function: evidence from a longitudinal study. *Nephrol. Dial. Transplant.* **18**, 797–803 (2003).
30. Asghar, R. B. & Davies, S. J. Pathways of fluid transport and reabsorption across the peritoneal membrane. *Kidney Int.* **73**, 1048–1053, https://doi.org/10.1038/ki.2008.32 (2008).
31. Liu, J. H. et al. Association between pulse pressure and peritoneal transport status in patients undergoing peritoneal dialysis. *Perit. Dial. Int.* **30**, 362–366, https://doi.org/10.3747/pdi.2009.0016 (2010).
32. Pang, W., Yang, X., Bargman, J. M. & Oreopoulos, D. G. Association between pulse pressure and mortality in patients undergoing peritoneal dialysis. *Perit. Dial. Int.* **29**, 163–170 (2009).
33. Wanner, C., Amann, K. & Shoji, T. The heart and vascular system in dialysis. *Lancet* **388**, 276–284, https://doi.org/10.1016/s0140-6736(16)30508-6 (2016).
34. Hassan, K. et al. The impact of sub-clinical overhydration on left ventricular mass in peritoneal dialysis patients. *Int. J. Clin. Exp. Med.* **8**, 5890–5896 (2015).
35. Unver, S. et al. Correlation between hyperhydration, left ventricular hypertrophy and fibroblast growth factor 23 in hemodialysis patients. *Ren. Fail.* **37**, 951–956, https://doi.org/10.3109/0886022x.2013.1052945 (2015).
36. Acci, G. et al. Volume control associated with better cardiac function in long-term peritoneal dialysis patients. *Perit. Dial. Int.* **26**, 85–88 (2006).
37. McGowan, J. H. & Cleland, J. G. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am. Heart J.* **146**, 388–397, https://doi.org/10.1016/j.amhearts.2006.07.016 (2003).
38. Hensen, L. C. R. et al. Prevalence of left ventricular systolic dysfunction in pre-dialysis and dialysis patients with preserved left ventricular ejection fraction. *Eur. J. Heart Fail.* **20**, 560–568, https://doi.org/10.1016/j.ejhf.2017.05.018 (2018).
39. Unger, E. D. et al. Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction. *Eur. J. Heart Fail.* **18**, 103–112, https://doi.org/10.1002/ejhf.445 (2016).
40. Liu, Y. W. et al. Association of left ventricular longitudinal strain with mortality among stable hemodialysis patients with preserved left ventricular ejection fraction. *Clin. J. Am. Soc. Nephrol.* **8**, 1564–1574, https://doi.org/10.2215/CJN.10671012 (2013).
41. Cooper, B. A. et al. Comparing different methods of assessing body composition in end-stage renal failure. *Kidney Int.* **58**, 408–416, https://doi.org/10.1046/j.1523-1755.2000.00180.x (2000).
42. Chamney, P. W. et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am. J. Clin. Nutr.* **85**, 80–89, https://doi.org/10.1093/ajcn/85.1.80 (2007).

**Acknowledgements**

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2018R1C1B5045006, 2019R1F1A1062663). The authors also wish to acknowledge the grant funded by Research Foundation of Physician, The Catholic University of Korea of 2017 and the financial support of the Catholic Medical Center Research Foundation made in the program year of 2018.

**Author contributions**

Y. Kim, Y.A. Hong, and G.J. Ko planned studies. H.E. Yoon, B.S. Choi, S.J. Shin, Y. Kim, S.Y. Lee, S. Lee, S.H. Kim, E.Y. Lee, S.K. Sin and Y.J. Kwon were involved in patient recruitment and performed studies. J.H. Kim, Y.K. Chang and S.Y. Kim. collated and analyzed data. J.E. Kim and S.Y. Ahn performed statistical analysis. Y.A. Hong wrote the manuscript. G.J. Ko offered progressive review when the manuscript was being written.

**Competing interests**

The authors declare no competing interests.

**Additional information**

**Correspondence** and requests for materials should be addressed to G.J.K.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.