

Impact of Ultrafiltration on Serum Sodium Homeostasis and its Clinical Implication in Patients With Acute Heart Failure, Congestion, and Worsening Renal Function

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Background—The relationship between changes in serum sodium with clinical events in acute heart failure patients using different decongestive events has not been investigated. This study aimed to describe changes in serum sodium levels during decongestion therapy in patients receiving stepped pharmacological therapy versus ultrafiltration.

Methods and Results—We studied 188 patients who were enrolled in the CARRESS-HF trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure). Treatment-induced hyponatremia was defined as admission normonatremia (≥ 135 mEq/L) with a subsequent decrease (< 135 mEq/L) during hospitalization. Patients treated with ultrafiltration had significantly lower sodium levels than those with conventional treatment at days 1, 4, and 7 (all $P < 0.01$), whereas those at day 30 were similar between the groups. Changes in sodium levels in patients with ultrafiltration were negatively correlated to those in serum creatinine and plasma renin activity. The incidence of treatment-induced hyponatremia was significantly higher in the ultrafiltration group than those receiving conventional treatment ($P = 0.002$). Although patients with discharge hyponatremia had a higher risk for composite end point of all-cause death, rehospitalization, or unscheduled hospital visit in comparison to those without (adjusted hazard ratio, 2.01; 95% confidence interval, 1.09–3.70; $P = 0.025$), the risk was comparable between patients with treatment-induced hyponatremia and those who did not experience any hyponatremia (adjusted hazard ratio, 0.99; 95% confidence interval, 0.50–1.96; $P = 0.99$).

Conclusions—Fluid removal by ultrafiltration was associated with a decrease in serum sodium levels compared with diuretic treatment but returned to baseline levels at day 30. Discharge hyponatremia but not treatment-induced hyponatremia was associated with worse clinical outcomes.

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Key Words: creatinine ■ diuretics ■ heart failure ■ hyponatremia ■ ultrafiltration

Treatment for acute decompensated heart failure (ADHF) is often complicated by electrolyte abnormalities, which have commonly been considered side effects of diuretic therapy rather than limiting the efficacy of decongestion.¹ The natriuretic effect of conventional diuretic therapy contributes to neurohumoral activation,² which can cause an imbalance between water retention and excretion and leads to hyponatremia.^{3,4} Hyponatremia in the setting of heart failure (HF) has been known as a marker of increased disease severity and a predictor of short- and long-term morbidity and mortality in patients with impaired or unimpaired left ventricular systolic function.^{5,6}

intravascular volume without activation of the neurohumoral axis, leading to fewer electrolyte imbalances than diuretics.^{10,11} However, data are limited on changes in serum sodium levels between ultrafiltration and a more conventional treatment strategy in ADHF patients. Accordingly, we aimed to describe serum sodium levels at baseline and discharge, as well as changes in serum sodium during decongestion therapy. We also investigated the relationship between these values with outcomes in patients who developed worsening renal function despite persistent congestion after ADHF who received stepped pharmacological therapy versus ultrafiltration.

See Clinical Perspective

Ultrafiltration has been used as an effective alternative approach to reduce volume overload in ADHF patients resistant to conventional diuretic treatment.^{7–9} Theoretically, isotonic plasma water removal by ultrafiltration preserves

Methods

Study Population

The study design and primary results of the CARRESS-HF trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure)

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have been reported in detail.^{12,13} Briefly, the CARRESS-HF trial was a prospective, randomized, controlled trial that assessed the effects of ultrafiltration compared with a stepped pharmacological therapy strategy in patients hospitalized with ADHF and evidence of cardio-renal syndrome with persistent congestion. The trial was conducted from June 2008 to January 2012 at 22 sites and included 188 patients. Patients were eligible if they were admitted with a primary diagnosis of ADHF regardless of left ventricular ejection fraction. Patients also were required to have had worsening renal function (defined as an increase in serum creatinine concentration of at least 0.3 mg/dL within 12 weeks before or 10 days after ADHF admission) and persistent congestion. Patients were excluded who had a serum creatinine concentration >3.5 mg/dL at admission or who required vasoactive medications. Ultrafiltration was performed at a fluid removal rate of 200 mL per hour, and intravenous diuretic therapy was placed on a urine output-guided stepped pharmacological approach to provide a comparable measure of fluid removal to ultrafiltration, 3 to 5 L per day.¹⁴ This study was approved by the Heart Failure Network Steering, Protocol Review, and Data Safety Monitoring Committees and was approved by each participating site's institutional review board. All patients provided written informed consent.

Sodium Measurements and Study End Points

Patients in the trial had serial laboratory measurements measured at the study sites. The serum sodium concentrations and serum creatinine were measured at baseline, at days 1, 2, 3, 4, and 7 during hospitalization, and days 30 and 60 after discharge. Plasma renin activity (PRA) was measured at baseline and 4, 7, and 60 days after randomization. Treatment-induced hyponatremia (TIH) was defined as admission normonatremia (≥ 135 mEq/L) with a subsequent decrease (< 135 mEq/L) during hospitalization. Decompensation hyponatremia was defined as admission hyponatremia (< 135 mEq/L) that disappeared with decongestive treatment at discharge. Discharge hyponatremia was defined as hyponatremia (< 135 mEq/L) at discharge or day 7. The postdischarge composite end point included all-cause mortality, rehospitalization, and unscheduled clinic and emergency department visits.¹²

Statistical Analysis

Categorical variables are shown as numbers and percentages and were compared using the χ^2 test or the Fisher exact test, as appropriate. Continuous variables are expressed as mean and SD or median and interquartile range where appropriate. On the basis of their distribution, continuous variables were compared using the Student *t* test or Wilcoxon rank-sum test. Two-sided *P* values < 0.05 were considered statistically significant. Mixed effects modeling with unstructured covariance was used to compare the association of pharmacological therapy or ultrafiltration with serum sodium levels over time. The Kaplan–Meier method was used to estimate cumulative event-free survival, and differences in the survival curves were compared via the log-rank test. A multivariable Cox proportional hazards model was constructed to estimate the adjusted hazard ratio (HR) and 95% confidence interval (CI). Candidate variables for the multivariable model were selected when their *P* values in univariable analysis were < 0.10 or based on their clinical relevance. These included age, sex, ischemic cause, left ventricular ejection fraction, hypertension, diabetes mellitus, hyperlipidemia, creatinine, hemoglobin, albumin, and PRA. All statistical analyses were performed with the statistical software program JMP Pro 10.0.0 (SAS Institute Inc, Cary, NC) and Stata 13.1 (StataCorp, College Station, TX).

Results

Patient Characteristics

The mean patient age was 68 ± 13 years, 75% were male, and the mean left ventricular ejection fraction was $37 \pm 18\%$. A total of 47 (25%) patients had hyponatremia at admission, whereas 141 (75%) patients had normonatremia at admission

(Figure 1). Among 141 patients who had normonatremia at admission, 46 (33%) patients had TIH during their hospital stay. Among 47 patients with hyponatremia at admission, 18 patients had normonatremia at discharge, whereas 29 patients had persisting hyponatremia at discharge. Baseline characteristics that were stratified by the admission hyponatremia and the patterns of changes in sodium levels during decongestion therapy are shown in Table 1. The prevalence of TIH was significantly higher in the ultrafiltration group than in those in the pharmacological therapy group (47% versus 22%; $P=0.002$; Figure I in the Data Supplement). Table 2 shows the comparison of baseline characteristics between patients with and without discharge hyponatremia. Patients with discharge hyponatremia had significantly lower plasma osmolarity than those without discharge hyponatremia. There were no significant differences in use of thiazide diuretics among the groups.

Changes in Serum Sodium Concentration: Pharmacological Therapy Versus Ultrafiltration

The mean serum sodium concentration at baseline, days 1, 2, 3, 4, 7, 30, and 60 was 137.2 ± 4.1 , 137.3 ± 4.1 , 136.9 ± 4.4 , 136.4 ± 4.4 , 135.9 ± 4.7 , 135.6 ± 4.4 , 137.1 ± 4.5 , and 137.8 ± 3.4 mEq/L, respectively. Figure 2 compares the changes in serum sodium concentrations between patients in the pharmacological therapy and those with ultrafiltration. The mean serum sodium levels were significantly lower in the ultrafiltration group than those in the pharmacological therapy group at baseline (137.8 ± 4.2 versus 136.6 ± 4.0 mEq/L; $P=0.03$), day 1 (138.1 ± 3.9 versus 136.4 ± 4.1 mEq/L; $P=0.004$), day 2 (138.3 ± 4.1 versus 135.5 ± 4.3 mEq/L; $P<0.001$), day 3 (137.8 ± 3.9 versus 135.0 ± 4.4 mEq/L; $P<0.001$), day 4 (137.7 ± 3.7 versus 134.1 ± 4.8 mEq/L; $P<0.001$), and day 7 (137.1 ± 3.6 versus 134.2 ± 4.6 mEq/L; $P<0.001$), respectively. However, there were no significant differences in sodium levels between the groups at day 30 (137.6 ± 4.5 versus 136.6 ± 4.5 mEq/L; $P=0.08$) and day 60 (138.0 ± 3.4 versus 137.5 ± 3.4 mEq/L; $P=0.21$). In comparison to pharmacological therapy, ultrafiltration significantly impacted sodium levels over time ($P<0.001$; Figure 2). There were no significant differences in weight changes from baseline to day 4 between the ultrafiltration and the pharmacological therapy (-12.6 ± 8.6 versus -12.5 ± 11.5 kg; $P=0.99$), nor among 4 groups stratified by patterns of sodium changes (normonatremia, -12.6 ± 11.1 kg; TIH, -11.5 ± 8.6 kg; decompensation hyponatremia, -15.3 ± 11.4 kg; and persistent hyponatremia, -12.2 ± 8.7 kg; $P=0.64$).

Correlation of Changes in Serum Sodium Levels With Other Biomarkers

The mean serum creatinine in patients with ultrafiltration at baseline and days 1, 2, 3, 4, 7, 30, and 60 were 2.02 ± 0.64 , 2.07 ± 0.70 , 2.16 ± 0.81 , 2.29 ± 1.00 , 2.41 ± 1.14 , 2.10 ± 1.21 , 1.96 ± 0.80 , and 1.91 ± 0.84 mg/dL, respectively. The mean PRA in patients with ultrafiltration at baseline, days 4, 7, and 60 were 11.5 ± 13.0 , 23.6 ± 35.2 , 20.1 ± 29.7 , and 12.5 ± 21.2 ng per mL per hour, respectively. Figure 3 illustrates changes in serum sodium, serum creatinine, and PRA. In patients with ultrafiltration, both serum creatinine levels and PRA were increased along with decongestion therapy and peaked at day 4, then returned to baseline levels at day 30. These changes were negatively correlated

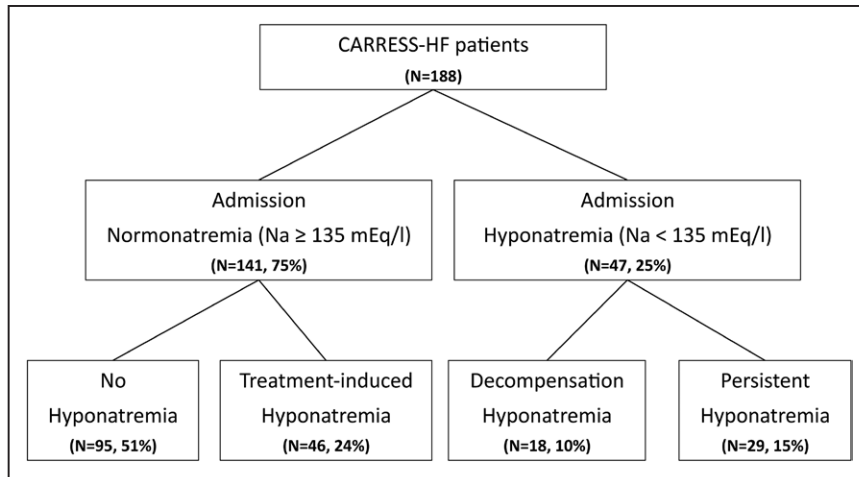


Figure 1. Study patient flow. Treatment-induced hyponatremia (TIH) was defined as admission normonatremia with a subsequent decrease during hospitalization. Decompensation hyponatremia was defined as admission hyponatremia that disappeared with decongestive treatment at discharge. CARRESS-HF indicates Cardiorenal Rescue Study in Acute Decompensated Heart Failure.

with those in serum sodium levels (Figure 3A). In contrast, changes in serum sodium, creatinine, and PRA were relatively stable in patients with conventional therapy (Figure 3B).

Sodium Levels and Postdischarge Clinical Events

Overall, there were 29 (15.4%) deaths, 83 (44.1%) rehospitalizations after discharge, and 32 (17.0%) unscheduled hospital visits

without admission. The median follow-up was 58 days (interquartile range, 51–63 days). There were 46 patients (24.4%) with hyponatremia at discharge. Patients with discharge hyponatremia had greater event rates than those without discharge hyponatremia (HR, 1.62; 95% CI, 1.02–2.58; $P=0.042$). Even after adjusting for confounders, the excess risk of patients with discharge hyponatremia relative to those without for the outcome remained

Table 1. Patient Characteristics Stratified by Patterns of Changes in Sodium Levels During Decongestion Therapy

Variable	No Hyponatremia (n=95)	Treatment-Induced Hyponatremia (n=46)	Decompensation Hyponatremia (n=18)	Persistent Hyponatremia (n=29)	P Value
Clinical characteristics					
Age, y	68±14	68±13	68±14	67±10	0.96
Male	68 (72)	36 (78)	15 (83)	22 (76)	0.67
Body weight, lb	240.7±77.5	232.1±71.0	216.3±50.5	223.6±73.4	0.48
Ischemic cause	39 (41)	15 (33)	8 (44)	12 (41)	0.74
Ejection fraction, %	39.5±18.0	37.8±16.9	30.9±13.4	34.2±18.8	0.19
Hypertension	85 (89)	39 (85)	11 (61)	24 (83)	0.02
Diabetes mellitus	64 (67)	28 (61)	11 (61)	21 (72)	0.72
Hyperlipidemia	81 (85)	34 (74)	11 (61)	18 (62)	0.02
Ultrafiltration	33 (35)	29 (63)	10 (56)	22 (76)	<0.001
Baseline laboratory measures					
Sodium, mEq/L	139.8±2.7	137.3±1.9	132.5±1.7	131.2±2.9	<0.001
Potassium, mEq/L	4.2±0.6	4.1±0.5	4.1±0.5	4.2±0.6	0.77
Blood urea nitrogen, mg/dL	51.0±19.8	58.3±26.7	50.6±22.1	62.7±27.8	0.06
Creatinine, mg/dL	2.24±0.56	2.24±0.58	2.15±0.53	2.10±0.58	0.67
Hemoglobin, g/dL	10.9±1.7	10.9±1.8	11.1±2.1	11.3±1.9	0.79
Albumin, g/dL	3.3±0.5	3.6±0.5	3.3±0.7	3.3±0.5	0.06
Plasma renin activity, ng mL ⁻¹ h ⁻¹	8.1±11.0	15.0±20.0	25.0±45.7	21.9±30.0	0.003
Plasma osmolarity, mOsm/L	303.8±7.1	300.2±5.5	289.6±6.9	289.7±6.7	<0.001
Baseline medication					
ACE inhibitor or ARB	42 (44)	18 (39)	6 (33)	14 (48)	0.72
β-blockers	75 (79)	37 (80)	13 (72)	22 (76)	0.89
Thiazide	20 (21)	10 (22)	5 (28)	9 (31)	0.68

Values are n (%) or mean±SD. ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor antagonist.

Table 2. Patient Characteristics and Clinical Outcomes: Patients With Versus Without Discharge Hyponatremia

Variable	Discharge Hyponatremia (+), n=46	Discharge Hyponatremia (-), n=88	P Value
Age, y	68±11	66±14	0.30
Male	36 (78)	64 (73)	0.48
Ischemic cause	28 (61)	48 (55)	0.48
Left ventricular ejection fraction, %	39.1±18.5	36.3±16.9	0.37
Ultrafiltration	29 (63)	33 (35)	0.002
Hypertension	39 (85)	76 (86)	0.80
Diabetes mellitus	33 (71)	58 (66)	0.49
Dyslipidemia	31 (67)	68 (77)	0.22
Baseline laboratory measures			
Sodium, mEq/L	134.1±3.8	138.4±3.8	<0.001
Creatinine, mg/dL	2.24±0.58	2.24±0.56	0.98
Blood urea nitrogen, mg/dL	60.8±24.6	52.3±23.0	0.05
Plasma renin activity, ng mL ⁻¹ h ⁻¹	18.9±26.3	10.3±14.4	0.02
Plasma osmolarity, mOsm/L	295.2±7.5	300.8±9.1	<0.001
Primary outcomes			
All-cause mortality	11 (24)	7 (8)	0.01
Rehospitalization	23 (52)	36 (41)	0.22
Unscheduled hospital visit	7 (16)	12 (14)	0.73

Values are n (%) or mean±SD.

significant (adjusted HR, 2.01; 95% CI, 1.09–3.70; $P=0.025$; Figure 4A). The risks for the outcomes were neutral between patients with and without admission hyponatremia (adjusted HR, 1.64; 95% CI, 0.96–2.80; $P=0.07$; Figure 4B). The adverse event rates in patients who developed TIH were comparable to

those who did not experience any hyponatremia (adjusted HR, 0.99; 95% CI, 0.50–1.96; $P=0.99$; Figure 4C). Although there were no significant differences in mortality among the 4 groups ($P=0.27$; Figure 4D), patients with TIH had significantly lower mortality than patients with persistent hyponatremia (adjusted HR, 0.43; 95% CI, 0.19–0.97; $P=0.041$; Figure 4E). Although outcomes after discharge were comparable among TIH patients between ultrafiltration versus pharmacological therapy, patients with persistent hyponatremia in the ultrafiltration group had significantly worse outcomes than those in the pharmacological therapy group ($P=0.024$).

Discussion

The current analysis of the CARRESS-HF trial investigated the changes in serum sodium levels during hospitalization and after discharge and its association with treatment strategies (ultrafiltration versus stepped pharmacological therapy), in 188 patients hospitalized with ADHF, irrespective of left ventricular ejection fraction, who had renal dysfunction and persistent signs of congestion. The major findings of this study were as follows: (1) serum sodium levels in patients with ultrafiltration were decreased during decongestive therapy but returned to baseline levels at 30 days after discharge. In contrast, changes in sodium levels in patients with pharmacological therapy were relatively stable, (2) changes in serum sodium levels during decongestive therapy inversely correlated with changes in serum creatinine and PRA, and (3) TIH was observed in 24.5% of the patients, but TIH was not associated with excessive event rates, although discharge hyponatremia had a significant prognostic value for adverse events.

Hyponatremia in HF is a common electrolyte disorder and is associated with an increased risk for short- and long-term mortality.^{5,6} The pathophysiology of hyponatremia in HF has been thought to be dilutional in most cases, and sodium depletion is relatively rare without loop or thiazide diuretics.^{15–17} However, it is difficult to differentiate these 2 categories, and overlap likely exists. In HF, decreased cardiac output leads to the activation of baroreceptors, which in turn activates the sympathetic nervous system, the renin–angiotensin–aldosterone system, and the release of nonosmotic arginine vasopressin.

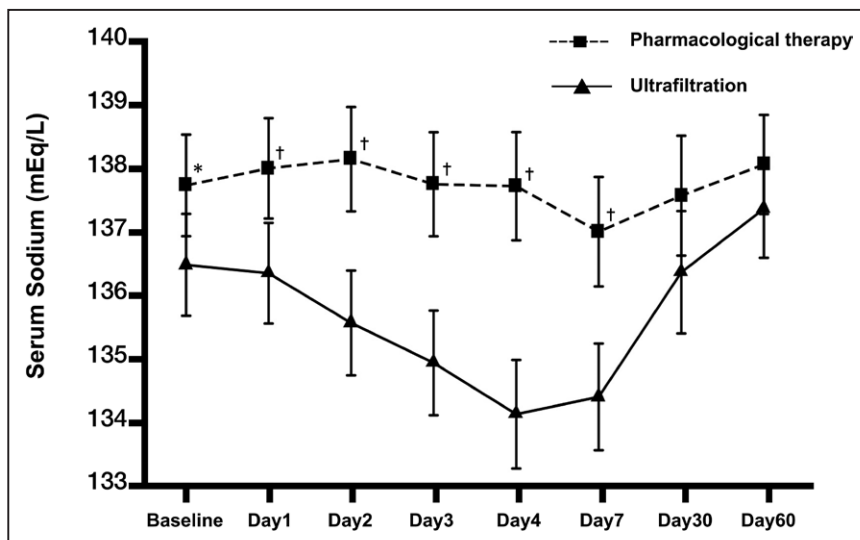


Figure 2. Comparison of changes in serum sodium levels between patients on pharmacological therapy vs ultrafiltration. * $P<0.05$, † $P<0.01$.

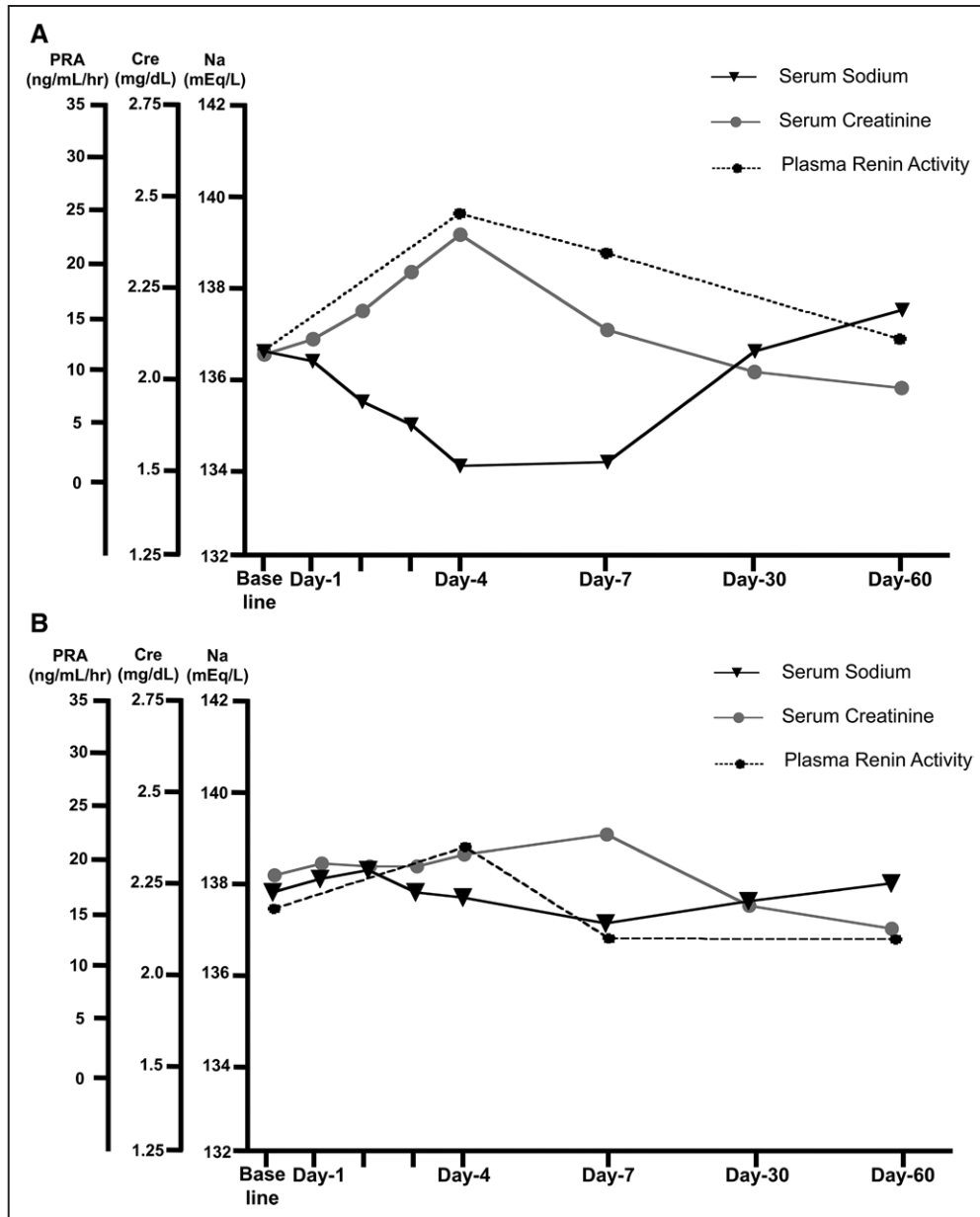


Figure 3. Comparison of changes in serum sodium, creatinine, and plasma renin activity (PRA) in patients receiving ultrafiltration (A) and those with pharmacological therapy (B).

These maladaptive responses limit solute and free water delivery to the distal segments of the nephron which ensures maximal free water absorption and leads to hyponatremia.^{18,19} The natriuretic effect of conventional diuretic therapy also significantly contributes to the development of hyponatremia in HF.^{1,2} In addition, hyponatremia was found to be more prevalent in ADHF patients with renal dysfunction.²⁰ A decreased glomerular filtration rate results in diminution in the amount of fluid delivered to the distal tubule and limits the rate of renal water excretion.²¹

Ultrafiltration can remove isotonic fluid without affecting effective circulating volume, leading to decreased neurohumoral activity.⁷⁻⁹ Dilutional hyponatremia is a condition in which intravascular volume is increased and the total amount of sodium is not depleted. Therefore, inappropriate

intravascular fluid retention leads to a low serum sodium concentration. If patients had pure dilutional hyponatremia, sodium levels increase along with fluid removal by decongestion therapy. In fact, tolvaptan, a vasopressin type 2 receptor antagonist, shows an increase in serum sodium levels in ADHF with hyponatremia.²² Ultrafiltration can remove a higher amount of sodium in addition to isotonic fluid in contrast to diuretics treatment which only removes hypotonic fluid. Theoretically, if patients had only dilutional hyponatremia, a more favorable water and salt balance can be achieved by ultrafiltration.⁹ However, we found that patients with ultrafiltration had a significant decrease in sodium levels during decongestion therapy compared with those with diuretic therapy. This unexpected result could be explained by patients having depletion or mixed dilutional and

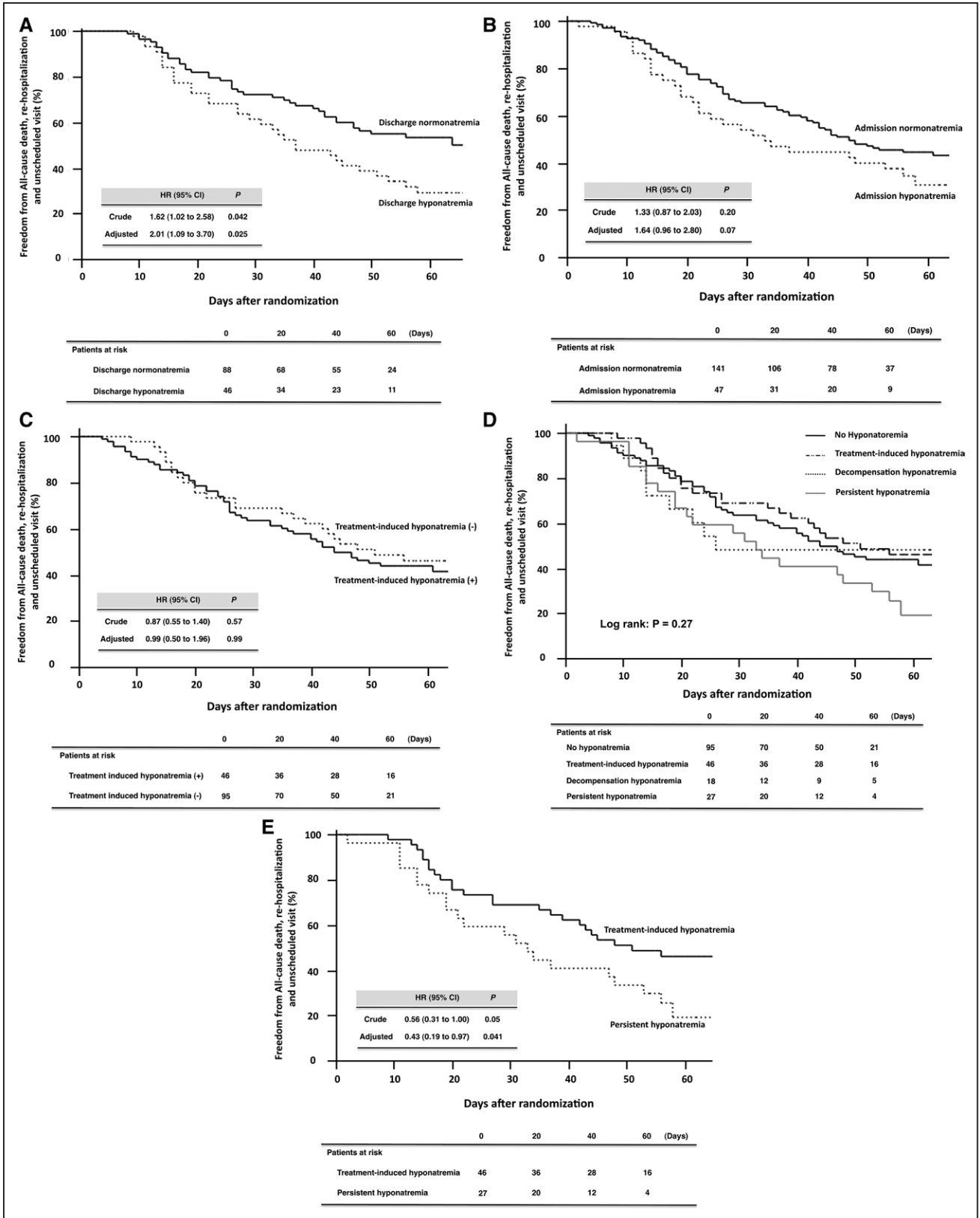


Figure 4. Comparison of Kaplan-Meier survival curves for freedom from the primary outcome measures between patients with and without discharge hyponatremia (A), those with and without admission hyponatremia (B), those with and without treatment-induced hyponatremia (C), among patients stratified by patterns of sodium levels during decongestion therapy (D), and those with persistent hyponatremia vs treatment-induced hyponatremia (E). CI indicates confidence interval; and HR, hazard ratio.

depletional hyponatremia. Higher amount of sodium removal by ultrafiltration could worsen hyponatremia in those patients. Therefore, decreasing sodium levels during decongestion therapy may suggest coexisting sodium depletion even if patients had signs of residual congestion. It is, however, difficult to predict these sodium changes or diagnose underlying sodium depletion before decongestion therapy. In this study, patients with admission hyponatremia were thought to have dilutional hyponatremia because those patients had signs of residual congestion and lower plasma osmolality than those without. Another explanation for the decrease in sodium levels by ultrafiltration may be related to the fluid removal rate. If an isotonic fluid removal rate by ultrafiltration is too fast to refill intravascular sodium from extracellular interstitial space, this could lead to reducing circulating volume and sodium depletion. This phenomenon may be seen with other methods of fluid removal. Continuous ambulatory peritoneal dialysis is associated with higher sodium removal than automated peritoneal dialysis thought to be related to longer dwell times despite equal daily fluid removal.^{23,24} Our finding that serum creatinine levels and PRA were increased in parallel with the decreasing sodium levels supports this hypothesis. Of note, the baseline plasma osmolality was similar between patients with pharmacological therapy and ultrafiltration. Further studies are needed to diagnose or differentiate these 2 different, but often overlapped, conditions of hyponatremia.

Several clinical studies have shown that hyponatremia is a predictor of rehospitalization and short- and long-term mortality in subjects hospitalized with HF.^{5,6} Our findings are consistent with previous studies that have demonstrated patients with discharge hyponatremia and were associated with poor outcomes.²⁵ Recently, Verbrugge et al²⁶ investigated the temporal pattern of hyponatremia development during decongestion therapy. The authors reported that TIH was observed in 14.3% of the patients in ADHF. In this study, TIH was observed in 24.5% of patients. Consistent with the previous studies, patients with TIH had similar outcomes compared with those who did not experience any hyponatremia during the treatment.²⁶ More advanced chronic kidney disease patients may explain a higher prevalence of TIH in our study. Development of TIH is not necessarily a bad sign unless hyponatremia persists after decongestion therapy; however, care is needed for their potential risks to persistent hyponatremia because patients who developed TIH may have coexisting sodium depletion. Further research is unquestionably needed to identify a subphenotype of HF patients with hyponatremia based on the physiological response to decongestion therapy or sodium loading.

This study has several limitations inherent to its design. First, the number of patients studied and the trial duration may be insufficient to assess the relationships between sodium levels and postdischarge outcomes. However, CARRESS-HF trial was a unique study performed by a volume-targeted decongestion strategy which enabled us to investigate the relationships between intravascular volume and serum sodium levels across the decongestion strategies. Second, this was a post hoc analysis from a randomized clinical trial with the inherent associated limitations. Despite covariate adjustment, we cannot exclude the influence of other measured and

unmeasured confounders. Third, plasma levels of vasopressin were not available in this study, which could be insightful to assess changes in effective arterial blood volume or volume depletion. Assessment of urine osmolality and sodium were not available in this study either, although these are important to know whether the hyponatremia is because of excess renal excretion of sodium relative to water. Finally, weight gain before hospitalization and blood pressure changes during the decongestion therapy was not available.

Conclusions

Fluid removal by ultrafiltration was associated with significant decrease in serum sodium levels compared with diuretic treatment but return to baseline levels at day 30. Although discharge hyponatremia was associated with worse clinical outcomes, patients with TIH had similar outcomes to those without.

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Disclosures

None.

References

- Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med.* 1965;39:442–451.
- Marti CN, Khan H, Mann DL, Georgiopoulou VV, Bibbins-Domingo K, Harris T, Koster A, Newman A, Kritchevsky SB, Kalogeropoulos AP, Butler J; Health ABC Study. Soluble tumor necrosis factor receptors and heart failure risk in older adults: Health, Aging, and Body Composition (Health ABC) Study. *Circ Heart Fail.* 2014;7:5–11. doi: 10.1161/CIRCHEARTFAILURE.113.000344.
- Sica DA. Hyponatremia and heart failure—treatment considerations. *Congest Heart Fail.* 2006;12:55–60.
- Sica DA. Sodium and water retention in heart failure and diuretic therapy: basic mechanisms. *Cleve Clin J Med.* 2006;73(suppl 2):S2–S7; discussion S30–S33.
- Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation.* 1986;73:257–267.
- Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF Jr, Califf RM, Gheorghiu M; OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation.* 2005;111:2454–2460. doi: 10.1161/01.CIR.0000165065.82609.3D.
- Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, Mackedanz S, Sobotka PA, Schollmeyer M, Goldsmith SR. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol.* 2005;46:2043–2046. doi: 10.1016/j.jacc.2005.05.098.
- Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49:675–683.

9. Giglioli C, Landi D, Cecchi E, Chiostrì M, Gensini GF, Valente S, Ciaccheri M, Castelli G, Romano SM. Effects of ULTRAFiltration vs. DiureticS on clinical, biohumoral and haemodynamic variables in patients with deCompensated heart failure: the ULTRADISCO study. *Eur J Heart Fail*. 2011;13:337–346. doi: 10.1093/eurjhf/hfq207.
10. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiadè M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail*. 2005;11:200–205.
11. Mentz RJ, Felker GM. Noncardiac comorbidities and acute heart failure patients. *Heart Fail Clin*. 2013;9:359–367, vii. doi: 10.1016/j.hfc.2013.04.003.
12. Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, Chen HH, Rouleau JL, Givertz MM, Semigran MJ, Mann D, Deswal A, Bull DA, Lewinter MM, Braunwald E. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Card Fail*. 2012;18:176–182. doi: 10.1016/j.cardfail.2011.12.009.
13. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304. doi: 10.1056/NEJMoa1210357.
14. Grodin JL, Stevens SR, de Las Fuentes L, Kiernan M, Birati EY, Gupta D, Bart BA, Felker GM, Chen HH, Butler J, Dávila-Román VG, Margulies KB, Hernandez AF, Anstrom KJ, Tang WH. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. *J Card Fail*. 2016;22:26–32. doi: 10.1016/j.cardfail.2015.07.007.
15. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342:1581–1589. doi: 10.1056/NEJM200005253422107.
16. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577–585. doi: 10.1056/NEJM199908193410806.
17. McKie PM, Schirger JA, Costello-Boerrigter LC, Benike SL, Harstad LK, Bailey KR, Hodge DO, Redfield MM, Simari RD, Burnett JC Jr, Chen HH. Impaired natriuretic and renal endocrine response to acute volume expansion in pre-clinical systolic and diastolic dysfunction. *J Am Coll Cardiol*. 2011;58:2095–2103. doi: 10.1016/j.jacc.2011.07.042.
18. Dzau VJ. Renal and circulatory mechanisms in congestive heart failure. *Kidney Int*. 1987;31:1402–1415.
19. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol*. 2015;65:480–492. doi: 10.1016/j.jacc.2014.12.010.
20. Aronson D, Darawsha W, Promyslovsky M, Kaplan M, Abassi Z, Makhoul BF, Goldberg A, Azzam ZS. Hyponatraemia predicts the acute (type 1) cardio-renal syndrome. *Eur J Heart Fail*. 2014;16:49–55. doi: 10.1093/eurjhf/hft123.
21. Schrier RW, Berl T. Nonosmolar factors affecting renal water excretion (first of two parts). *N Engl J Med*. 1975;292:81–88. doi: 10.1056/NEJM197501092920207.
22. Shanmugam E, Doss CR, George M, Jena A, Rajaram M, Ramaraj B, Anjaneyan K, Kanagesh B. Effect of tolvaptan on acute heart failure with hyponatremia—a randomized, double blind, controlled clinical trial. *Indian Heart J*. 2016;68(suppl 1):S15–S21. doi: 10.1016/j.ihj.2015.07.006.
23. Khandelwal M, Kothari J, Krishnan M, Liakopoulos V, Tziviskou E, Sahu K, Chatalalsingh C, Bargman J, Oreopoulos D. Volume expansion and sodium balance in peritoneal dialysis patients. Part II: Newer insights in management. *Adv Perit Dial*. 2003;19:44–52.
24. Fourtounas C, Hardalias A, Dousdampanis P, Papachristopoulos B, Savidaki E, Vlachoianis JG. Sodium removal in peritoneal dialysis: the role of icodextrin and peritoneal dialysis modalities. *Adv Perit Dial*. 2008;24:27–31.
25. Gheorghiadè M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med*. 2007;167:1998–2005. doi: 10.1001/archinte.167.18.1998.
26. Verbrugge FH, Grodin JL, Mullens W, Taylor DO, Starling RC, Tang WH. Transient hyponatremia during hospitalization for acute heart failure. *Am J Med*. 2016;129:620–627. doi: 10.1016/j.amjmed.2016.01.016.

CLINICAL PERSPECTIVE

Hyponatremia is a common electrolyte disorder and a therapeutic challenge in heart failure and may be a side effect of diuretic therapy. On the other hand, ultrafiltration has been thought of as an effective alternative approach to mechanically reduce congestion which may be resistant to conventional diuretic treatment. In comparison to diuretic use, it has been thought to have less activation of the neurohormonal axis and fewer electrolyte imbalances. However, data are limited on changes in serum sodium levels between ultrafiltration and conventional diuretic therapy. In this post hoc analysis of the CARRESS-HF trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), contrary to expectations, we observed a greater reduction in serum sodium with ultrafiltration versus pharmacological therapy, which was negatively correlated to corresponding serum creatinine and plasma renin activity. The prompt resolution of serum sodium levels after discharge may indicate the electrolyte depletion by ultrafiltration. Furthermore, although patients with discharge hyponatremia had a higher risk for composite end point of all-cause mortality, rehospitalization, or unscheduled hospital visits in comparison to those without, the risk was comparable between patients with treatment-induced hyponatremia and those who did not experience any hyponatremia. These findings highlight the need to differentiate 2 different conditions of hyponatremia, dilutional versus depletion, and to refine a slower ultrafiltration regimen to avoid overaggressive mechanical removal of salt and water.

Impact of Ultrafiltration on Serum Sodium Homeostasis and its Clinical Implication in Patients With Acute Heart Failure, Congestion, and Worsening Renal Function

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Correction

In the article by Kitai et al, “Impact of Ultrafiltration on Serum Sodium Homeostasis and its Clinical Implication in Patients With Acute Heart Failure, Congestion, and Worsening Renal Function,” which appeared in the February 2017 issue of the journal (*Circ Heart Fail.* 2017;10:e003603. DOI: 10.1161/CIRCHEARTFAILURE.116.003603), several corrections are needed.

In Figure 1, the number of patients with admission hyponatremia should be 47, not 46. In addition, a prior version of Figure 2 was inadvertently published instead of the final version.

In the abstract, “adjusted hazard ratio, 1.66; 95% confidence interval, 1.03–2.65; $P=0.037$ ” should read “adjusted hazard ratio, 2.01; 95% confidence interval, 1.09–3.70; $P=0.025$ ” and “adjusted hazard ratio, 0.93; 95% confidence interval, 0.57–1.51; $P=0.76$ ” should read “adjusted hazard ratio, 0.99; 95% confidence interval, 0.50–1.96; $P=0.99$.”

In the text, on page 4, “adjusted HR, 2.01; 95% CI, 1.09–3.70; $P=0.041$ ” should read “adjusted HR, 2.01; 95% CI, 1.09–3.70; $P=0.025$.”

The authors regret these errors.

These corrections have been made to the current online version of the article, which is available at <http://circheartfailure.ahajournals.org/content/10/2/e003603>.

SUPPLEMENTAL MATERIAL

Supplementary Figure 1.

Comparison of the distribution of patients with no hyponatremia, treatment induced hyponatremia, decompensation hyponatremia and persistent hyponatremia between patients with pharmacological therapy versus ultrafiltration.

