Brief Report

Biochemical Determinants of Changes in Plasma Volume After Decongestion Therapy for Worsening Heart Failure

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ABSTRACT

Background: Optimal vascular volume is required to avoid organ dysfunction during decongestive therapy for worsening heart failure (HF). This study investigated the relation between changes in serum substance(s) and the vascular volume after diuresis in HF patients.

Methods and Results: Data from 47 patients with HF undergoing conventional diuretic therapy were analyzed. Blood tests included measurements of hemoglobin, hematocrit, and serum albumin/solutes. The relative changes in the plasma volume (%PV) from worsening HF to recovery were determined with the use of the Strauss formula. When divided into 2 groups based on the median %PV, the group with preserved volume (%PV $\geq -10\%$, range -10% to 21%; n = 23) exhibited a smaller decrease in body weight (-2.50 ± 1.98 vs -4.29 ± 2.60 kg; $P = .012$) and serum sodium (Na) (-1.57 ± 3.29 vs -4.13 ± 4.96 mEq/L; $P = .04$) and chloride (Cl) (-2.0 ± 4.06 vs -6.79 ± 5.21 mEq/L; $P = .001$) concentrations and a smaller increase in albumin (0.20 ± 0.28 vs 0.41 ± 0.24g/dL; $P = .009$) compared with the group with nonpreserved volume (%PV $< -11\%$, range -33% to -11%; n = 24) after decongestive therapy. Changes in %PV were positively correlated with changes in body weight ($r = 0.406$; $P = .0047$) and serum Na ($r = 0.433$; $P = .0024$) and Cl ($r = 0.408$; $P = .0044$) concentrations and negatively correlated with changes in albumin ($r = -0.492$; $P = .0004$), blood urea nitrogen ($r = -0.306$; $P = .037$), and creatinine ($r = -0.306$; $P = .036$). Multivariate logistic regression analysis demonstrated an independent association between preserved %PV and an increased or preserved serum Cl concentration after decongestive therapy (odds ratio 8.71, 95% confidence interval 1.20−63.0; $P = .032$).

Conclusions: Positive and independent association exists between change in the vascular volume and the serum Cl concentration under decongestive HF therapy. (*J Cardiac Fail 2019;25:213−217*)

Key Words: Heart failure, Chloride, Diuretics, Plasma volume, Renal function.

The pathophysiologic background of the biochemical determinants of vascular volume in heart failure (HF) status is unclear. Recent preliminary studies reported that vascular expansion under worsening HF is independently associated with changes in serum chloride (Cl) concentration, and the consequence of these changes and vascular expansion might be related to different phenotypes of clinical HF.[1,2] The present study examined the relationship of the changes between serum substance(s) and vascular volume to determine whether or not the "chloride theory"[1,2] is applicable to HF pathophysiology during diuretic therapy for worsening HF.

Methods

The present study was a substudy of a recently published study[3] focusing on monitoring HF patients. Informed consents were obtained from all of the patients before study enrollment. The patients were asked about changes in symptoms and examined for the appearance of physical signs of fluid retention during each visit to the clinic. Additional routine tests included ultrasonographic detection of the pleural effusion,[4] monitoring of weight changes,[5] and measurement of serum B-type natriuretic peptide. Peripheral blood tests, chest x-ray, electrocardiography, and

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Manuscript received November 14, 2017; revised manuscript received September 20, 2018; revised manuscript accepted September 30, 2018.

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A version of this study was presented in part at the ESC 2016 Conference, Rome.

See page 216 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2018.09.014

echocardiography were performed at study entry and at a clinic visit during follow-up after an appropriate interval.

Blood tests included measurements of hemoglobin, hematocrit, total protein, albumin, serum electrolytes (sodium [Na], potassium, and Cl), blood urea nitrogen, and creatinine. The percentage shift in the plasma volume (%PV) under a change in HF status was estimated by means of the Strauss method.[1]

Criteria for selecting the event of worsening HF included the appearance of at least 2 of the following HF-related signs: physical signs (the third heart sound, pulmonary crackles, leg edema), fluid weight gain (≥1.5 kg), and pleural effusion on ultrasound. Worsening HF was treated with the use of conventional diuretics and appropriate use of inotropic drugs in the hospital or outpatient clinic.

All data are expressed as mean ± SD for continuous data and percentage for categoric data. Paired and unpaired *t* tests for continuous data and Fisher exact tests for categoric data were used for 2-group comparisons. Pearson correlation was performed to evaluate the association between the changes in %PV and changes in body weight, peripheral blood, and blood chemistry under decongestive therapy. Logistic regression analysis with the use of the dichotomous dependent variables was applied to determine the independent predictors of changes in %PV under decongestive therapy by selecting variables that demonstrated a significant linear association with change in %PV. The threshold for entry of variables into the model was $P < .05$. The odds ratio (OR) and associated 95% confidence interval (CI) were estimated to determine the association between those variables and change in the %PV. A P value of $< .05$ was considered to be statistically significant.

Results

Ambulatory patients with HF (n = 83) were enrolled and followed at the outpatient clinic; of these, 47 had data available for the analysis in the present study. The characteristic features of the 47 patients with clinical stability at study entry are presented in Supplemental Table 1. The interval between worsening HF and its recovery after decongestive therapy was 27.8 ± 19.8 days (range 8−59 days).

The distribution of changes in %PV from worsening HF to its recovery in the 47 study patients is shown in Fig. 1. The incidences of increase and decrease in %PV were 6 (13%) and 41 (87%), respectively, after therapy. As presented in Table 1, among a total of 47 worsening HF events, changes in %PV were positively correlated with changes in body weight and serum Na and Cl (Supplemental Fig. 1) concentrations and negatively correlated with changes in serum albumin, blood urea nitrogen, and creatinine.

As presented in Supplemental Table 2, the group with preserved volume (%PV ≥ −10%, range −10% to 21%; n = 23) exhibited a smaller decrease in body weight and serum Na and Cl concentrations and a smaller increase in hemoglobin, hematocrit, and albumin than the group with nonpreserved volume (%PV < −11%, range −33% to −11%; n = 24) after decongestive therapy. The group with preserved plasma volume also exhibited a tendency toward preserved renal function, defined by a smaller increase in the serum creatinine concentration.

Multivariate logistic regression analysis (Table 2) demonstrated an independent association between preserved %PV and an increased or preserved serum Cl concentration

Table 1. Correlation Between Changes in Percentage Shift in the Plasma Volume and Changes in Multiple Variables in Recovery From Worsening Heart Failure

Variable	*r*	*P* Value
Body weight (kg)	0.406	.0047*
Serum log BNP (pg/mL)	0.276	.061
Serum albumin (g/dL)	−0.492	.0004*
Serum sodium (mEq/L)	0.433	.0024*
Serum potassium (mEq/L)	−0.284	.053
Serum chloride (mEq/L)	0.408	.0044*
Blood urea nitrogen (mg/dL)	−0.306	.037*
Serum creatinine (mg/dL)	−0.306	.036*

BNP, B-type natriuretic peptide.
*Statistically significant.

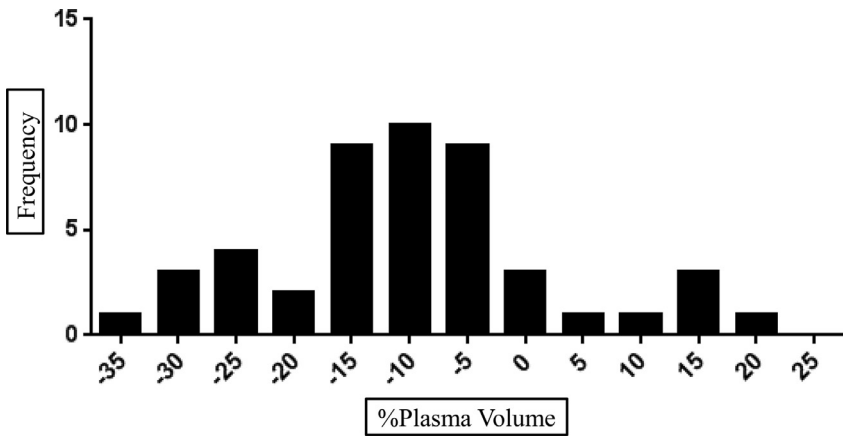

Fig. 1. Distribution of the percentage shift in the plasma volume from worsening heart failure to its recovery in the 47 study patients.

Table 2. Multivariate Predictors of Changes in Percentage Shift in the Plasma Volume (%PV) After Decongestive Therapy

Factor	%PV		Wald chi-square	Odds Ratio (95% CI)	*P* Value
	Preserved (n = 23)	Nonpreserved (n = 24)			
Body weight loss					
≥3 kg	8	15	0.961	0.497 (0.12−2.01)	.327
<3 kg	15	9			
Serum albumin					
≥0.5 g/dL	5	11	3.45	0.141 (0.02−1.11)	.063
<0.5 g/dL	18	13			
Serum sodium					
Increased	10	7	0.06	1.23 (0.24−6.37)	.808
No change or decreased	13	17			
Serum chloride					
Increased	10	2	4.59	8.71 (1.20−63.0)	.032*
No change or decreased	13	22			
Blood urea nitrogen					
≥10 mg/dL	8	11	1.66	4.12 (0.48−35.4)	.198
<10 mg/dL	15	13			
Serum creatinine					
≥0.3 mg	5	8	2.08	0.203 (0.023−1.78)	.15
<0.3 mg	18	16			

*Statistically significant.

after decongestive therapy (OR 8.71, 95% CI 1.20−63.0; $P = .032$).

Discussion

Interpretation of the Present Study

Recent studies indicated that serum Cl is a key electrolyte that regulates plasma volume during worsening HF.[1,2] Adding to this observation, the present study provides preliminary support for a novel finding of a positive and independent association between vascular volume and the serum Cl concentration after decongestive therapy, suggesting that the proposed "chloride theory" for worsening HF[1,2] could be analogically applicable to HF pathophysiology during the resolution of worsening HF by means of diuretic therapy. Taking together the present observations and the established central role of Cl in the renin-angiotensin-aldosterone system (RAAS),[6,7] an additional hypothesis for the "chloride theory" for the resolution of worsening HF is proposed here that states that the changes in the serum Cl concentration are the primary determinant of changes in the plasma volume, RAAS, and antidiuretic hormone system under decongestive therapy for worsening HF, as summarized in Supplemental Fig. 2.

General Consideration of Diuretic Therapy for Worsening HF

Careful attention to changes in the vascular volume is crucial in decongestive therapy for worsening HF because either residual vascular congestion or excess depletion of vascular volume affects the clinical picture and course of HF.[8,9] Physiologically, fluid overload results in tissue edema. Impaired oxygen and metabolic diffusion, distorted tissue architecture, obstruction of capillary blood flow and lymphatic drainage, and disturbed cell-cell interactions may then contribute to progressive organ dysfunction.[10] The ideal cascades of decongestion with the use of diuretic therapy for HF patients[7,11] are a continuous process of removing the extravasated fluid at the interstitial and third spaces[12,13] by the venous and lymphatic systems, pumping it out from the body via the cardiorenal system, and eventually regaining individualized euvolemic status to retain adequate arterial and ventricular filling in relation to cardiac function and to relieve venous congestion in each HF patient. The present study gives preliminary support for a potential central role of chloride for determining the plasma volume presumably through its effect on vascular tonicity,[14] suggesting that chloride manipulation may be an essential therapeutic target in HF treatment, as described below.

Decongestion Therapy for Worsening HF Based on the "Chloride Theory"

In addition to the integrity of both cardiac and renal function,[8] expansion of the intravascular volume is an important determinant of diuresis[15] under diuretic therapy for HF. Therefore, plasma volume[1,2,13] or hemoconcentration[9,16] should be monitored as part of the clinical assessment of HF patients. Notably, it should be kept in mind that changes in the plasma volume are heterogeneously distributed among HF patients during resolution of worsening HF, as shown in Fig. 1, and therefore it is important to individually evaluate change in plasma volume or hemoconcentration in relation to the clinical features, particularly regarding whether there is residual congestion or excess vascular depletion already during diuretic therapy.

Based on the "chloride hypothesis" for HF pathophysiology, manipulation of the serum Cl concentration could

become an attractive therapeutic target for HF treatment, such as reducing the quantity and concentration of serum Cl with the use of conventional diuretics for HF worsening with a higher concentration and retention of serum Cl (Supplemental Fig. 2A)[17,18] and preserving and enhancing the concentration of serum Cl by means of aquaresis with the use of a V_2-receptor antagonist (Supplemental Fig. 2B)[19–21] or supplementing Cl with the use of hyperosmotic saline infusion[22,23] for worsening HF with decreased serum Cl concentration (Supplemental Fig. 2C). Diuretic treatment with the use of a carbonic anhydrase inhibitor (acetazolamide), as described in earlier articles,[24,25] is a potent agent for "Cl-regaining diuretics." Recent studies reconfirmed that Cl manipulation with the use of acetazolamide could be an essential diuretic strategy for HF treatment.[26–28]

Diuretic therapy for the retention or supply of Cl in the plasma may sometimes induce residual cardiac volume overload in relation to cardiac function, thus ensuring a persistent burden on the diseased heart. Indeed, administration of a vasopressin receptor antagonist removes fluid with spared or improved renal blood flow and glomerular filtration rate compared with the administration of a loop diuretic,[21] but the aquaretic effects of vasopressin receptor blockade often produce a chronic burden on a patient's heart after therapy.[29] In this regard, preserving serum Cl retention while maintaining plasma volume[19] may be another possible explanation for the failure of tolvaptan to improve ventricular remodeling and cardiovascular outcome,[30] aside from a potential adverse effects of V1a stimulation.[29] In the case of a persistent cardiac burden even under adequate diuretic therapy for unloading the heart, strategies to further reduce the cardiac burden or enhance cardiac power would be required.[11]

Study Limitations

This study was performed with a small number of patients at a single center. Accordingly, statistical power may be particularly low for multivariate analyses, in which wide CIs were obtained. Interpretation of those analyses must be done with great caution. Further well designed large trials are required to confirm the findings of the present study.

Conclusion

This pilot study supported the validity of the "chloride theory" for worsening HF[1,2] to HF pathophysiology under resolution of worsening HF by decongestion therapy.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2018.09.014.

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