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SHORT COMMUNICATION

Mechanistic insights into chloride-related heart failure progression according to the plasma volume status

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Abstract

Aims Two types of heart failure (HF) progression were recently proposed on the basis of an increased vs. non-increased serum chloride concentration. The applicability of this concept to real-world HF pathophysiology requires further investigation. The present study evaluated the mechanisms of HF progression to a different type according to changes in the estimated plasma volume status (ePVS).

Methods and results Data from 47 patients (32% men; 78.2 ± 9.7 years of age) with stable to worsening HF (37.5 ± 16 days) were analysed. Physical examination, standard blood tests, and b-type natriuretic peptide (BNP) measurements were conducted. The ePVS was calculated as follows: ePVS (dL/g) = [100 − haematocrit (%)]/[haemoglobin (g/dL)]. For the study subjects as a whole (n = 47), changes in the ePVS correlated positively with changes in the serum chloride concentration from stable to worsening HF (r = 0.398, P = 0.0056). When divided into two groups of worsening HF with an increased (n = 31) vs. non-increased serum chloride concentration (n = 16), no significant baseline differences in body weight, serum logBNP, or ePVS were detected between groups. Under worsening HF, the increase in body weight (2.34 ± 1.12 vs. 2.59 ± 1.56 kg, P = 0.57) and logBNP (0.39 ± 0.30 vs. 0.54 ± 0.31 pg/mL, P = 0.13) did not differ between groups, but the increase in the ePVS was smaller in the group with a non-increased serum chloride concentration compared with that with an increased serum chloride concentration (0.292 ± 0.49 vs. 0.653 ± 0.60 dL/g, P = 0.044). An increase in the %change in ePVS $\geq$ 10% was less common in patients with a non-increased chloride concentration (37% vs. 71%, P = 0.03). Patients with a non-increased serum chloride concentration had more HF signs (3.31 ± 0.79 vs. 2.65 ± 0.71, P = 0.005) and a higher incidence of pulmonary rales (63% vs. 16%, P = 0.0024) than those with an increased serum chloride concentration.

Conclusions According to the changes in the ePVS, HF progression may result from a difference between two HF types (i.e. increased vs. non-increased serum chloride concentration) in the cardiac reserve in response to a given cardiac burden by modulating plasma volume status via the possible tonicity potential of chloride.

Keywords Heart failure; Pathophysiology; Chloride; Body fluid; Vascular volume

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Introduction

Recent studies indicate that the electrolyte chloride greatly contributes to the plasma volume status in heart failure (HF) pathophysiology.[1,2] The 'chloride theory' for HF pathophysiology,[3] a unifying hypothesis coupling the central role of the electrolyte chloride in the tubuloglomerular feedback mechanism with the fluid distribution in the human body, was recently proposed (Supporting Information, *Figure S1*). The applicability of this theory to real-world HF pathophysiology requires further investigation.

The plasma volume status at any time point can be easily estimated by the index of the estimated plasma volume status (ePVS) according to the haemoglobin and haematocrit levels.[4,5] The present study aimed to gain insight into the mechanisms of the two types of HF progression defined by

'chloride theory',[3,6] that is, increased vs. non-increased serum chloride concentration, on the basis of changes in the ePVS from stable to worsening HF.

Methods

The present study is a sub-study of previously published studies[1,2,6] investigating the role of chloride in HF pathophysiology performed at the cardiology clinic of Nishida Hospital. Details of the study protocol, including selection of subjects, physical examination, and blood and device tests for evaluation of HF status, are described elsewhere.[1,2,6] In brief, eligible patients had at least one decompensated HF episode that resulted in hospitalization or outpatient treatment with conventional diuretics. At study entry, patient characteristics, history, and primary aetiology were recorded. The study patients were examined for the appearance of physical signs of fluid retention, pleural effusion by ultrasound, changes in the fluid status monitored using a digital body weight scale, and serum b-type natriuretic peptide (BNP) levels.[7] Peripheral haematologic and biochemical tests were performed by standard laboratory techniques. The ePVS during the HF clinical course was calculated at one time point according to Duarte's formula[4] as follows: ePVS (dL/g) = [100 − haematocrit (%)]/[haemoglobin (g/dL)].

Criteria for selecting the event of worsening HF included the appearance of at least two of the following HF-related signs, whether or not changes in symptoms occurred: physical signs (the third heart sound, pulmonary crackles, and leg oedema), fluid weight gain (≥1.5 kg), and pleural effusion on ultrasound.[1,2,6]

Statistical analyses

All data are expressed as a mean ± standard deviation for continuous data and percentage for categorical data. Paired and unpaired *t*-tests for continuous data and Fisher's exact test for categorical data were used for two-group comparisons. Pearson's correlation was performed to evaluate the association between changes in the serum chloride concentration and changes in ePVS. A P value < 0.05 was considered statistically significant.

Results

Ambulatory patients with HF (n = 83) were enrolled and followed up at the outpatient clinic of Nishida Hospital; of these, 47 had data available for analysis in the present study. The demographic features of the 47 patients with clinical stability at study entry are summarized in *Table 1*. The interval between clinical stability to worsening HF was 37.5 ± 16 days (range: 14–67 days). The cumulative number of HF-related signs/tests per patient was 2.87 ± 1.52 (range: 2–5).

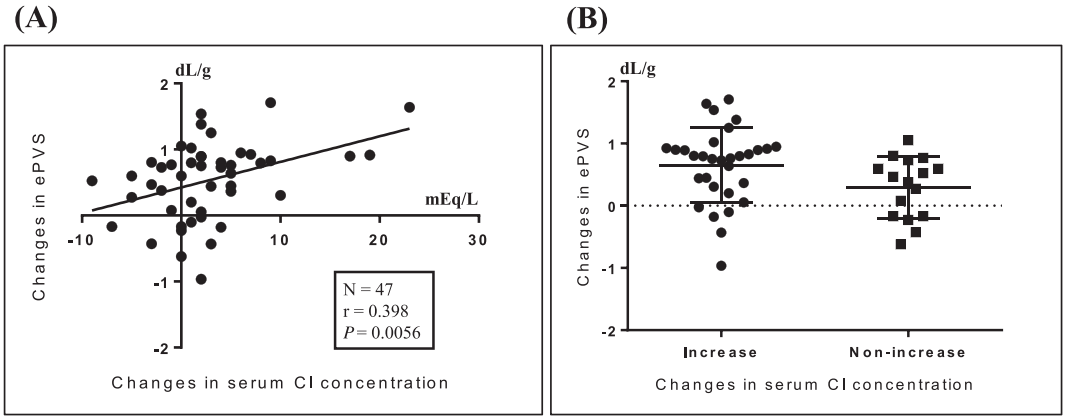
Table 1 Clinical characteristics of the study patients

Characteristics	n = 47
Age (years)	78.2 ± 9.7 (29–93)
Male	15 (32)
Primary cause of heart failure	
Hypertension	25 (53)
Valvular	8 (17)
Cardiomyopathy	6 (13)
Ischaemic	3 (6)
Arrhythmia	3 (6)
Congenital	2 (4)
Left ventricular EF (%)	56 ± 14
Left ventricular EF > 50%	25 (53)
Atrial fibrillation	16 (34)
NYHA-FC at stable period	
II/III	34 (72)/13 (28)
Medication	
Diuretics	46 (98)
Loop diuretics	31 (66)
Thiazide diuretics	24 (51)
Potassium-sparing diuretics	38 (81)
ACE inhibitors/ARB	30 (64)
Calcium antagonists	21 (45)
Beta-blockers	19 (40)
Digitalis	5 (11)
Nitrates	3 (6)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; EF, ejection fraction; NYHA-FC, New York Heart Association functional class.
Data are presented as number (%) of patients otherwise specified.

For the study subjects as a whole (n = 47), changes in the ePVS correlated positively with changes in the serum chloride concentration from stable to worsening HF (r = 0.398, P = 0.0056; *Figure 1A*). When patients were divided into two groups of worsening HF with an increased (n = 31) vs. non-increased serum chloride concentration (n = 16; *Table 2*), no significant differences in baseline body weight, serum logBNP, and ePVS were detected between groups. Under worsening HF from stability, the body weight (2.34 ± 1.12 vs. 2.59 ± 1.56 kg, P = 0.57) and serum logBNP (0.39 ± 0.30 vs. 0.54 ± 0.31 pg/mL, P = 0.13) also did not differ between groups, but the increase in the ePVS was smaller in the HF group with a non-increased serum chloride concentration compared with that with an increased serum chloride concentration (0.292 ± 0.49 vs. 0.653 ± 0.60 dL/g, P = 0.044; *Figure 1B*). An increase in the %change in ePVS ≥ 10% from stable to worsening HF (*Table 2*) was less common in patients with a non-increased chloride concentration (37% vs. 71%, P = 0.03). Under worsening HF (*Table 2*), patients with a non-increased serum chloride concentration had more physical signs of HF (3.31 ± 0.79 vs. 2.65 ± 0.71, P = 0.005) and a higher incidence of pulmonary rales (63% vs. 16%, P = 0.0024) than those with an increased serum chloride concentration.

Figure 1 (A) Relationship between changes in the serum chloride concentration and changes in the estimated plasma volume status (ePVS), and (B) comparison of changes in ePVS between groups with an increased vs. non-increased serum chloride concentration under stable to worsening heart failure.



Discussion

The present study provides a possible underlying mechanism for the two types of HF progression from stable to worsening HF, that is, increased vs. non-increased serum chloride concentration[1,3,6] according to the absolute changes in plasma volume estimated by Duarte's formula.[4] Namely, on the basis of changes in the ePVS, HF patients with an increased chloride concentration appear to have an adequate cardiac reserve by using the Frank–Starling mechanism[8] to deliver enough blood into the vascular space because of the higher ePVS from stable to worsening HF, and vice versa in those with a non-increased serum chloride concentration. How, then, do changes in the plasma volume status affect the chloride dynamics, and thus producing a different type of worsening HF?

Initiation of the cascade towards worsening HF in many cases could originate from a different cardiac reserve in response to a given cardiac burden. The HF patients with an adequate cardiac reserve could pump rich blood into the circulatory vascular space and preserve the effective blood volume,[9] whereas in contrast, HF patients with a poor cardiac reserve could not pump adequate blood into the vascular space, and thus, arterial circulatory integrity may be compromised because of insufficient cardiac power to deliver enough blood into the vascular space.[10] It is reasonable to consider that an ePVS with a smaller change from stable to worsening HF, which was observed in many HF patients with a non-increased chloride concentration in the present study, might activate renin-angiotensin-aldosterone system (RAAS) via a reduction in the effective blood volume status.[9] Importantly, enhanced activity of the RAAS and sympathetic nervous system would proceed to lower the serum chloride concentration by the following mechanisms suggested by Cuthbert *et al*.[11,12]: (i) bicarbonate resorption and chloride excretion in the proximal convoluted tubules under stimulation by adrenaline and angiotensin II and (ii) induction of metabolic alkalosis by secretion of H^+, bicarbonate gain, and excretion of chloride in the collecting ducts under aldosterone stimulation. A decrease in the serum chloride concentration would further promote the vicious cycle of enhanced activity of RAAS by further lowering of the urinary chloride supply to the macula densa cells in the kidney.[13,14] This sophisticated concept of the relationship between hypochloraemia and RAAS activity is conceivable and consistent with the 'chloride theory' for HF pathophysiology.[3,15,16] Although this study is observational and does not allow for causal inference, a change in the serum chloride concentration could be considered a representative adaptative mechanism of the dysfunctional heart to help unload its cardiac burden via modulating the plasma volume status by recruiting the tonicity potential of chloride to regulate the water distribution across body fluid compartments as following underlying mechanism. Chloride is thought to have tonicity potential and regulates water distribution across body compartments in the human body.[15,16] By this mechanism, body fluid in the vascular space (compartment) is thought to extravasate into the interstitial space (compartment) and induce a decrease in the effective blood volume in patients with worsening HF and a decreased serum chloride concentration, among whom many HF patients would present with auscultatory bilateral basal pulmonary rales (*Table 2*).

The ideal cascade of decongestion by diuretic therapy for HF patients is continuous removal of the extravasated fluid at the interstitial and third spaces by the venous and lymphatic systems, which is pumped out from the body via the cardio-renal system, and eventual regain of individualized intravascular euvolaemic status to retain adequate arterial and ventricular filling in relation to compromised cardiac function, and to relieve venous congestion.[15] Thus,

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Table 2 Changes in estimated plasma volume status between groups of increased vs. non-increased serum chloride concentration from stability to worsening of heart failure

	Changes in serum chloride concentration				
	Increase (n = 31)		Non-increase (n = 16)		P value
Symptom and physical signs at worsening heart failure					
Worsening of dyspnoea	15 (48%)		10 (63%)		0.54
Number of HF-related signs	2.65 ± 0.71		3.31 ± 0.79		0.005*
Body weight gain ≥ 1.5 kg	27 (87%)		15 (94%)		1
Bilateral pulmonary rales	5 (16%)		10 (63%)		0.0024*
Bilateral leg oedema	21 (68%)		12 (75%)		0.74
Third heart sound (S3)	7 (23%)		4 (25%)		1
Ultrasound pleural effusion	25 (81%)		12 (75%)		0.72
Serum chloride concentration (mEq/L)					
Stability	100 ± 5.29		103 ± 4.94		0.044*
Worsening	106 ± 4.22		101 ± 6.3		0.0038*
Δstability to worsening	5.45 ± 5.42		−2.6 ± 2.73		<0.0001*
P value	<0.0001		0.0019		
Body weight (kg)					
Stability	49.3 ± 13.5		50.8 ± 7.73		0.69
Worsening	51.9 ± 13.9		53.1 ± 7.6		0.75
Δstability to worsening	2.59 ± 1.56		2.34 ± 1.12		0.57
P value	<0.0001*		<0.0001*		
Serum logBNP (pg/mL)					
Stability	2.06 ± 0.43		2.12 ± 0.33		0.62
Worsening	2.60 ± 0.36		2.51 ± 0.28		0.41
Δstability to worsening	0.54 ± 0.31		0.39 ± 0.30		0.13
P value	<0.0001*		<0.0001*		
ePVS (dL/g)					
Stability	5.66 ± 1.32		5.60 ± 0.79		0.86
Range	(3.20 to 9.48)		(3.81 to 7.06)		
Worsening	6.32 ± 1.39		5.89 ± 0.91		0.28
Range	(3.17 to 8.52)		(3.89 to 8.11)		
ΔePVS	0.653 ± 0.60		0.292 ± 0.49		0.044*
Range	(−0.97 to 1.71)		(−0.62 to 1.05)		
P value	<0.0001*		0.032*		
%Change in ePVS from stability to worsening of heart failure					
Mean ± SD	11.9 ± 10.4		5.35 ± 8.35		0.032*
Range	(−10.2 to 35.8)		(−10.8 to 15.1)		
Distribution					
< −10%	1 (3%)	9 (29%)	1 (6%)	10 (63%)	0.03*
−10% to <0	4 (13%)		4 (25%)		
0 to <10%	4 (13%)		5 (31%)		
10% to <20%	18 (58%)	22 (71%)	6 (38%)	6 (37%)	
20%≦	4 (13%)		0		

BNP, b-type natriuretic peptide; ePVS, estimated plasma volume status; HF, heart failure; SD, standard deviation.
*Statistically significant ($P < 0.05$).

achievement of an individualized optimal plasma volume and resolution of congestion are two main purposes of diuretic therapy for controlling HF. Unrecognized hypervolaemia or a higher than ideal plasma volume, despite diuretic treatment to control HF, is deeply associated with a higher risk of an HF-related adverse outcome.[4,5,17,18] Accordingly, modulation of the plasma volume might be an attractive target for tailored patient care. In the setting of acute HF, achievement of an appropriate haemoconcentration with decongestion treatment is associated with a reduced risk of mortality, even with the induction of worsening of renal function.[19] The 'chloride theory' for HF pathophysiology[3,6] does not fully explain the complex HF pathophysiology, but in clinical practice at present, this theory could provide a primary care and management system for diuretic treatment of HF patients, with attention to the serum chloride concentration and changes central to this system.[15,16]

Anyway, additional studies are required to clarify the role of chloride in haemodynamic contribution to the HF pathophysiology,[15,16] such as evaluation of the concentrations of chloride in the different types of HF (e.g. HF with preserved vs. reduced ejection fraction) with different total cardiac burden and different cardiac functional reserve.

Conclusions

On the basis of changes in the ePVS, the differences in the progression of each type of HF, that is, increased vs.

non-increased serum chloride concentration,[1,3,6] may result from different cardiac reserve in response to a given cardiac burden, likely developing as a compensatory mechanism for the dysfunctional heart to unload its cardiac burden by modulating plasma volume status via the tonicity potential of the electrolyte chloride.[15,16]

Conflict of interest

The author has no conflicts of interest to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The 'chloride theory' for explaining fluid dynamics in the course of worsening heart failure. Solid line indicates enhanced supply or excitatory effect, and dotted line indicates reduced supply or inhibitory effect. *ADH* antidiuretic hormone, *Cl* chloride; *HF* heart failure, *Na* sodium, *RAAS* renin-angiotensin-aldosterone system.

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