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A chloride-centered approach for analyzing the association of changes in red blood cell and plasma volumes under worsening of heart failure

Abstract

Objective: The electrolyte chloride is the key electrolyte for regulating red blood cell volume and also plasma volume under transition of HF status, both from stability to worsening and recovery. The present study examined serum chloride concentration-centered association of the changes in red blood cell volume and plasma volume under transition of HF from stability to worsening of HF.

Subjects and methods: Data from 47 patients with acute HF were analyzed. Blood tests included measurements of hemoglobin, hematocrit, and serum albumin/solutes. Mean Red Blood Cell Volume (MCV) (fL) was calculated as hematocrit divided by the concentration of red blood cells multiplied by 10. The percent shift in the Plasma Volume (%PV) under stability to worsening HF was estimated by Straus method using two-point measurement of hemoglobin and hematocrit.

Results: As a whole of study subjects (n=47), there was no correlation between changes in %PV and changes in MCV (r=0.52, p=0.27). When stratified into two groups with increased (n=31) vs non increased serum chloride concentration (n=16) from stability to worsening HF, increase in %PV or MCV from stability to worsening HF was observed in 37/47 (79%) and 24/47 (51%) patients, respectively. Concordance changes of all of %PV, MCV, and serum chloride concentration toward increase appeared in 15 of 47 HF patients (32%), and those toward decrease in 3 (6%). Remaining 29 patients (62%) demonstrated discordance changes among %PV, MCV, and serum chloride concentration. There was no significant different between patients with concordance vs non-concordance of changes in %PV, MCV, and serum chloride concentration (χ^2=5.96, p=0.11).

Conclusion: There were no concordance changes among red blood cell volume, plasma volume, and serum chloride concentration from stable to worsening HF in the present study.

Keywords: Heart failure; Chloride; Plasma volume; Red blood cell volume.

Hajime Kataoka*

Internal Medicine, Nishida Hospital, Tsuruoka-Nishi-Machi 2-266, Saiki-City, Oita 876-0047, Japan.

***Corresponding Author:** **Hajime Kataoka**

Internal Medicine, Nishida Hospital, Tsuruoka-Nishi-Machi 2-266, Saiki-City, Oita 876-0047, Japan.

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Introduction

Red blood cell volume status has been a subject of clinical studies in Heart Failure (HF) [1-4]. The electrolyte chloride is the key electrolyte for regulating red blood cell volume [5] and also plasma volume [6] under transition of HF status, both from stability to worsening and recovery, i.e., moderate degree of positive linear association of changes in both red blood cell volume and plasma volume to the changes in serum chloride concentration. However, it is not clear whether concordance changes exist among changes in plasma volume, red blood cell volume, and serum chloride concentration under worsening of HF. Thus, the present study examined serum chloride concentration-centered association of the changes in red blood cell volume and plasma volume under transition of HF from stability to worsening of HF.

Material and methods

The present study is a sub-study of published previous studies [5-7] investigating the role of chloride in HF pathophysiology performed at the cardiology clinic of Nishida Hospital. Precise study protocol, including selection of subjects, physical examination, blood and device tests for evaluation of HF status are described elsewhere [5-7]. 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 etiology were recorded. The study patients were examined for the appearance of physical signs of fluid retention, searching for the ultrasound pleural effusion, monitoring changes in the fluid status using a digital body weight scale, and measuring b-type natriuretic peptide (BNP) levels [7]. Peripheral hematological and biochemical tests were performed by standard laboratory techniques. Mean Red Blood Cell Volume (MCV) (fL) was calculated as hematocrit divided by the concentration of red blood cells multiplied by 10. The percent shift in the Plasma Volume (%PV) under stability to worsening HF was estimated by Straus method using two-point measurement of hemoglobin and hematocrit [6]. 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, leg edema), fluid weight gain (≥1.5 kg), and pleural effusion on ultrasound [7].

Statistical analysis: All data are expressed as a mean ± SD for continuous data and percentage for categorical data. Fisher's exact test for categorical data were used for group comparisons. Pearson's correlation was performed to evaluate the association between %PV and changes in MCV. A *p* value less than 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±16.3 days (range: 14 - 67 days). The cumulative number of the appearance of HF-related signs/tests was 2.87±1.52 (range: 2-5).

As a whole of study subjects (n=47), there was no correlation between changes in %PV and changes in MCV (r=0.52, p=0.27; Figure 1). Table 2 shows concordance of changes between %PV and MCV according to the changes in serum chloride concentration, i.e., stratified into two groups with increased (n=31) vs

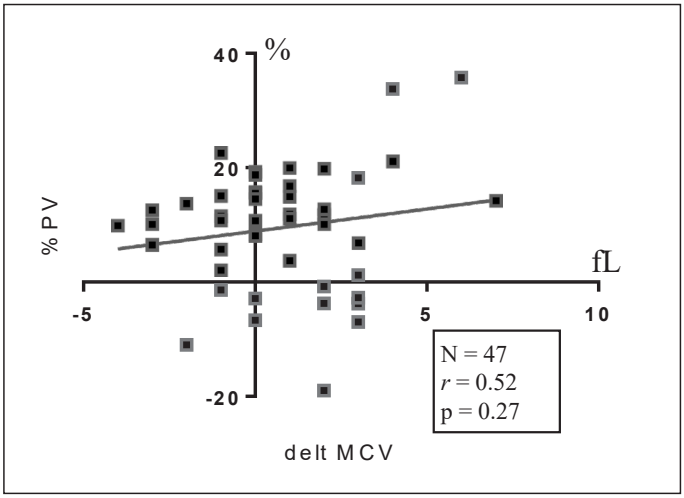

Figure 1: Relationship of the Changes between Mean Red Blood Cell Volume (MCV) and Plasma Volume (%PV) from Stability to Worsening Heart Failure.

Table 1: Relationship of the Changes between Mean Red Blood Cell Volume (MCV) and Plasma Volume (%PV) from Stability to Worsening Heart Failure.

Characteristics	n = 47
Age (years)	
Mean ± SD	78.2±9.7
Range	29–93
Male	15 (32)
Primary cause of HF	
Hypertension	25 (53)
Valvular	8 (17)
Cardiomyopathy	6 (13)
Ischemic	3 (6)
Arrhythmia	3 (6)
Congenital	2 (4)
Left ventricular EF (%)	
Mean ± SD	56 ± 14
Left ventricular EF > 50%	25 (53)
Atrial fibrillation	16 (34)
NYHA-FC at stable period	
II	34 (72)
III	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)

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

Table 2: Concordance of Changes in %PV and MCV according to the Changes in Serum Chloride Concentration from Stability to Worsening Heart Failure.

	Changes in Serum Chloride Concentration from Stability to Worsening Heart Failure		*p* value
	Increase of serum chloride concentration (n = 31)	Non-Increase of serum chloride concentration (n = 16)	
%PV↑/MCV↑	15	3	0.11 (χ^2=5.96)
%PV↑/MCV↓	11	8	
%PV↓/MCV↑	4	2	
%PV↓/MCV↓	1	3	

MCV: mean red blood cell corpuscular volume; %PV: percent change in plasma volume.

non-increased serum chloride concentration (n = 16), from stability to worsening HF. Increase in %PV or MCV from stability to worsening HF was observed in 37/47 (79%) and 24/47 (51%) patients, respectively. Concordance changes of all of %PV, MCV, and serum chloride concentration toward increase appeared in 15 of 47 HF patients (32%), and those toward decrease in 3 (6%). Remaining 29 patients (62%) demonstrated discordance changes among %PV, MCV, and serum chloride concentration. Thus, there was no significant different between patients with concordance vs non-concordance of changes in %PV, MCV, and serum chloride concentration (χ^2=5.96, *p*=0.11).

Discussion

Evaluation of red blood cell in HF pathophysiology seems to be important. In untreated HF patients, the total red blood cell volume is reported to be only 5% higher than that in controls [1]. Other studies [2,3] have demonstrated that the distribution of red blood cell mass in patients admitted to the hospital for worsening HF is heterogenous, and may be reduced or increased. The increase in red blood cell mass would contribute vascular expansion and could induce cardiac burden [3,4]. Mechanisms for changes in red blood cell mass in HF pathophysiology, however, are yet unknow. The chronically elevated erythropoietin by the kidney may one possible underlying mechanism for increase in red blood cell mass in HF patients [8]. Recent study [9] has reported that chloride is the key electrolyte for regulation of water movement across body fluid compartments [10], showing positive linear association of changes in both red blood cell volume [5] and also plasma volume [6,9] to the change in serum chloride concentration under worsening of HF. Accordingly, it could be expected that concordance volume changes both in red blood cell mass and plasma volume in concordance to change in serum chloride concentration under HF status. The findings of the present study have shown that increase in blood cell mass estimated by MCV occurred only in 24/47 (51%) of study patients, and unexpectedly, there was no concordance changes among red blood cell volume, plasma volume, and serum chloride concentration from stable to worsening HF.

Limitation: Insufficient statistic power might influence such a negative present result because of small sample size. Anyway, it should be kept in mind that red blood cell mass would be greatly affected by serum chloride concentration. Further studies are needed to determine clinical significance of red blood cell mass in HF pathophysiology, in particular its association of electrolyte chloride and its contribution to cardiac burden.

Disclosures: None.

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