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Vascular expansion during worsening of heart failure: Effects on clinical features and its determinants☆,☆☆

Hajime Kataoka

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

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ABSTRACT

Background: This study investigated the relation of the changes in serum solutes/albumin to the level of vascular expansion and clinical features during worsening HF.
Methods: Data from 47 patients with acute on chronic HF worsening were analyzed. Blood tests included hemoglobin, hematocrit, albumin, solutes (Na/K/Cl/BUN/Cr), and b-type natriuretic peptide (BNP). The relative change in the vascular expansion from stable to worsening HF was estimated based on changes in the plasma volume (%PV).
Results: When divided into two groups based on the median %PV, the clinical features of the expansion group (11 ≤ %PV [range 11% to 36%]; $n = 24$) included a lower incidence of crackles (13% vs. 52%, $p = 0.005$) and a tendency toward preserved renal function (83% vs. 57%, $p = 0.06$) compared with the non-expansion group (%PV [range −19% to 11%] < 11; $n = 23$), whereas the increase in body weight and log BNP did not differ between groups. The expansion group had a greater increase in serum Na (3.58 ± 4.43 vs. −0.11 ± 3.31 mEq/L, $p = 0.0016$) and Cl (5.54 ± 6.24 vs. −0.03 ± 4.18 mEq/L, $p = 0.0006$), and a decrease in serum albumin (−0.37 ± 0.3 vs. −0.16 ± 0.3 g/dL, $p = 0.04$) and creatinine (−0.28 ± 0.39 vs. −0.06 ± 0.22 mg/dL, $p = 0.027$) from stability to worsening HF. Multivariate logistic regression analysis revealed an independent association between the increase in %PV and the increase in the serum Cl concentration from stability to worsening HF (odds ratio: 12.2, 95% confidence interval: 1.78–83.8, $p = 0.011$).
Conclusions: Though this study is observational and does not allow for causal inference, it may nonetheless be speculated that a greater accumulation of Cl in the blood vessels acts to increase or maintain intravascular volume, which induces different clinical features of HF.

1. Introduction

Body fluid volume regulation is critically important for maintaining life. In patients with heart failure (HF), alterations in body fluid volume occur both extracellularly (including the interstitial fluid and intravascular volume) and intracellularly [1,2]. Body fluid regulation in health and disease is proposed to be through the arterial circulation, which is the primary body fluid compartment modulating renal sodium and water excretion [3,4]. Pathophysiologically important alterations in the sympathetic nervous system [5], the renin-angiotensin-aldosterone system (RAAS) [3,4], the vasopressin axis [6,7], and vasodilatory/natriuretic pathways [8] occur in HF. These disturbances are reflected at the renal circulation and tubular level, leading to the retention of sodium and water [3]. Body fluid retention during worsening of HF is usually accompanied by expansion of the intravascular volume [9–11]. It is unknown whether the clinical features differ according to the level of vascular expansion, and how changes in serum substance(s) are associated with changes in the intravascular volume. We tested the hypothesis that changes in serum solutes/albumin are associated with vascular expansion and induce different clinical features during worsening of HF.

2. Methods

2.1. Study population

The present study was a sub-study of a recently published study [12,13] focusing on monitoring body composition changes in established HF patients performed in the cardiology clinic of Nishida Hospital. Eligible patients had at least one decompensated HF episode that resulted in hospitalization or outpatient treatment with conventional diuretics. In the present analysis, HF patients with severe renal failure (serum creatinine concentration > 3.5 mg/dL at stable HF status) were excluded. Informed consent was obtained from all patients before study enrollment.

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☆☆ A version of this study was presented in part at the AHA 2015 held in Orlando.
E-mail address: hkata@cream.plala.or.jp.

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2.2. Study protocol

At study entry, patient characteristics, history, and primary etiology were recorded. The patients enrolled in this study were asked about changes in symptoms and examined for the appearance of physical signs of fluid retention [14] during each visit to the clinic by a clinician (H.K.). Additional routine tests included searching for the ultrasound pleural effusion [15], monitoring changes in the fluid status using a digital body weight scale incorporating a bioelectrical impedance analyzer (HBF-352-W, Omron Healthcare Co., Kyoto, Japan) [12,13,16], and measuring b-type natriuretic peptide (BNP) levels. Peripheral blood tests, chest X-ray, standard 12-lead electrocardiography, and echocardiography were performed at study entry and a clinic visit during follow-up after an appropriate interval.

2.3. Blood tests

Peripheral hematologic and biochemical tests, except BNP measurement, were not routinely obtained for all patients of the original study because that study did not focus on the correlation between HF status and blood chemistry. Thus, the patients and blood data of the present study were not selected consecutively, but were included based on the availability of a complete data set of both blood data and simultaneous HF-related clinical data at the time that the HF was clinically stable and worsening. Peripheral hematological and biochemical tests were performed by standard laboratory techniques. Blood tests included measurements of red cell count, hemoglobin (Hb), hematocrit (Ht), total protein, albumin, serum electrolytes (sodium, potassium, and chloride), blood urea nitrogen, and creatinine. The percent shift in the plasma volume (%PV) under a change in HF status was estimated from serial concomitant Hb and Ht concentrations according to the formula as shown in Fig. 1 [9,17].

2.4. Event of worsening HF

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. Worsening HF was treated by conventional therapy with a combination of loop diuretics, aldosterone blockade, thiazide diuretics, and/or inotropic drugs by oral and/or intravenous routes in the hospital or outpatient clinic.

In the event of multiple episodes of worsening HF in a single patient, the first episode was selected for the present analysis.

2.5. Statistical analysis

All data are expressed as a mean ± SD 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. Linear regression analysis with Spearman's coefficient was performed to evaluate relations among changes in %PV and changes in body weight, peripheral blood and its chemistry. Logistic regression analysis using the dichotomous dependent variables was used to determine the independent predictors of the changes in %PV during worsening HF by selecting variables that demonstrated a significant linear association with changes in the %PV and using iterative modeling procedures to arrive at the most efficient model. The threshold for entry of variables into the model was p value < 0.1. The odds ratio and associated 95% confidence interval were estimated to determine the association between those variables and the changes in %PV. A p value < 0.05 was considered statistically significant.

Table 1
Clinical characteristics of the study patients.

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.

3. 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. Diagnosis and precipitating factors of worsening HF status in 47 HF patients are shown in Table 2. The cumulative number of the appearance of HF-related signs/tests was 2.87 ± 1.52 (range: 2–5). The interval between clinical stability to worsening HF was 37.5 ± 16.3 days (range: 14–67 days).

The frequencies of %PV from clinical stability to worsening HF for the 47 study patients are shown in Fig. 2. From clinical stability to

$$\%\text{Change in plasma volume} = 100 \times \frac{\text{hemoglobin (stable)}}{\text{hemoglobin (worse)}} \times \frac{1-\text{hematocrit (worse)}}{1-\text{hematocrit (stable)}} - 100$$

Fig. 1. The equation for determining percent change in plasma volume (%PV) is derived from changes in the hemoglobin and hematocrit from clinical stability to worsening heart failure.

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