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ORIGINAL ARTICLE

Differences in extracellular fluid volume between acute heart failure patients with and without high systolic blood pressure

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Abstract

Aims Some reports have suggested that hypertensive acute heart failure (AHF) is caused by intravascular congestion, not interstitial congestion. We evaluated the differences in extracellular fluid volume assessed by bioelectrical impedance analysis (BIA) between AHF patients with and without high systolic blood pressure (sBP).

Methods This prospective single-centre study (UMIN000030266) included 178 patients hospitalized due to AHF between September 2017 and August 2018. We calculated extracellular water (ECW), intracellular water (ICW), total body water (TBW), and ECW-to-TBW ratio (oedema index: EI) by BIA and evaluated conventional parameters as follows: weight, *N*-terminal pro brain natriuretic peptide values, and echocardiography parameters on admission and before discharge. One-year outcomes included all-cause death and re-admission due to heart failure. We compared patients with sBP $>$ 140 mmHg on admission [clinical scenario 1 (CS1) group] and with sBP of $\leq$140 mmHg on admission (non-CS1 group).

Results The mean age of the patients was 79.5 ± 11.1 years, and 48.9% of the patients were female. EI on admission of 83 patients in the CS1 group was lower than that of 95 patients in the non-CS1 group. The change in EI from admission to before discharge was no significant in the CS1 group but was significant in the non-CS1 group. Comparing the changes from admission to before discharge between the CS1 and the non-CS1 group, delta ECW, delta ICW, delta TBW, and delta EI of the CS1 group were significantly smaller than those of the non-CS1 group. During the 1-year follow-up period after discharge of the 178 patients, the numbers of deaths and re-admissions due to acute HF were 26 (15%) and 49 (28%), respectively. Patients with high EI before discharge [$>$0.408 (median)] had significantly more cardiac events than patients with low EI [hazard ratio (HR): 2.15, 95% confidence interval (CI): 1.30–3.55]. Cox regression analysis revealed that higher EI as a continuous variable was significantly associated with worse outcome in non-CS1 group (HR: 1.46, 95% CI: 1.13–1.87), but not significantly associated with worse outcome in CS1 group (HR: 1.29, 95% CI: 0.98–1.69).

Conclusions EI on admission in patients with high sBP was not elevated, and changes in ECW, ICW, TBW, and EI in patients with high sBP were smaller than those in patients without high sBP. EI measured by BIA could distinguish AHF with interstitial or intravascular congestion.

Keywords Acute heart failure; High systolic blood pressure; Fluid volume; Oedema index

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Introduction

The majority of patients with heart failure (HF) have a combination of both intravascular congestion and tissue (interstitial) congestion.[1] Patients with predominant intravascular congestion have acute onset and do not require diuretics for treatment of HF.[2] On the other hand, patients with predominant interstitial congestion have a gradual progressive pulmonary and peripheral oedema.[3] Some reports have suggested that hypertensive HF defined as systolic blood

pressure (sBP) > 140 mmHg on admission is caused by intravascular congestion, not interstitial congestion.[4–6] Mebazaa *et al*. defined patients with dyspnoea and/or congestion with elevated sBP (>140 mmHg) as patients in clinical scenario 1 (CS1).[6] They reported that patients in CS1 are often systemically euvolaemic or hypovolaemic.

It is important to assess the quantity of fluid retention for treatment of HF. Bioelectrical impedance analysis (BIA) has been reported to be a useful tool for assessment of body composition in the fields of cardiology, hepatology, nephrology, and nutrition.[7] BIA is a non-invasive, safe, rapid, and simple method for evaluating body fluid volume. Cell membranes act as capacitors separating intracellular water (ICW) and extracellular water (ECW).[8] Electrical currents at low frequencies are insulated from the ICW, and ECW is thereby measured. However, electrical currents at high frequencies are able to pass through the cell membrane, meaning that both ICW and ECW, which comprise total body water (TBW), are measured.[9,10] Previous studies showed that data obtained by BIA were useful for treating HF.[11–13] In addition, several studies have suggested that oedema status, based on the ratio of ECW to TBW called oedema index (EI), is a factor indicating HF severity and prognosis of patients with HF.[14,15]

There is a lack of clinical data indicating the usefulness of EI for acute decompensated HF with high sBP on admission. The aim of this study was to evaluate differences in extracellular fluid volume assessed by BIA between acute heart failure (AHF) patients with and without high sBP.

Methods

Study design

This study (UMIN000030266) was a single-centre, prospective observational study designed to evaluate the usefulness of EI for estimating HF status and for predicting prognosis. This study was approved by the institutional ethics review committee of Tsuyama Chuo Hospital (approval number 325), and all patients provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki.

Participants

Patients admitted to Tsuyama Chuo Hospital due to AHF between September 2017 and August 2018 were enrolled. They had symptoms at admission and were diagnosed as having AHF with clinical and radiographic evidence of congestion. The exclusion criteria were age less than 20 years, lack of self-determination, HF with acute coronary syndrome, pulmonary thromboembolism, isolated right ventricular failure, septic shock, anaphylaxis shock, hypovolaemic shock, and implantation of a pacemaker, cardiac re-synchronization therapy device, or implantable cardioverter defibrillator.

Examinations

We calculated EI, the ratio of ECW to TBW obtained by BIA, and measured *N*-terminal pro-brain natriuretic peptide values (NT-proBNP) level, and we performed echocardiography on admission (acute phase) and before discharge (stable phase). Acute-phase examinations were performed within 7 days of admission. We evaluated differences before and after treatment in EI and conventional parameters: body weight, echocardiographic parameters including tricuspid regurgitation pressure gradient (TRPG) and diameter of the inferior vena cava during inspiration (IVCinsp) and log transformation of NT-proBNP (LogNT-proBNP). We compared the rates of changes in EI and conventional parameters in acute and stable phases.

BIA

BIA was performed with InBodyS10® (InBody Japan, Tokyo, Japan). Eight electrodes were attached to the patient's body: four on the dorsa of the wrists and the bases of the middle fingers and the other four on the anterior surfaces of the ankles and the bases of the middle toes.[9] Each patient lay in the supine position during BIA, with the legs kept shoulder-width apart and the arms slightly apart. In each patient, 30 impedance measurements were made by analysing the conductance of the electrical current across five body segments (each leg, each arm, and the trunk) at multiple frequencies (1, 5, 50, 250, 500, and 1000 kHz). Low frequencies pass through ECW but are unable to penetrate cell walls, thus enabling measurement of the water content outside cells. At higher frequencies, the water content within cells is also measured because higher frequencies can penetrate the cell walls. The use of multifrequency BIA enabled accurate estimation of the water contents inside and outside cells, allowing calculation of the ECW to TBW ratio as EI.

Body composition was analysed by height, weight, and impedance as the volumes of ECW, ICW, TBW, and fat. We did not set a specific time to perform BIA, and therefore, patients were analysed regardless of meals, excretion, and exercise timing.

Outcomes

We compared the rates of changes in EI and conventional parameters in acute and stable phases in overall patients. Then, the study population was divided into two groups depending on whether sBP on admission exceeded 140 mmHg: a

>140 mmHg group (CS1 group) and a ≤140 mmHg group (non-CS1 group). Changes in EI and conventional parameters from the acute phase to the stable phase were compared in those two groups.

In addition, we compared the ratios of cardiac events defined as all-cause death and re-admission due to acute HF within 1 year after discharge in patients with a discharge EI over the median value of each group and in patients with a discharge median less than the median value of each group.

Statistical analysis

Data are reported as means ± standard deviations for continuous variables and as values or percentages for categorical variables. Comparisons of parameters in the CS1 group and non-CS1 group were performed using Student's *t*-test or the chi-square test, as appropriate. Comparisons of parameters between the acute phase and stable phase were performed using the paired *t*-test in each group. The Kaplan–Meier method and Cox proportional hazard model were used to analyse the ratios of cardiac events including all-cause death and re-admission due to acute HF in patients in the two groups divided according to whether their EI exceeded the median EI in each group.

A *P* value of <0.05 was considered significant. Statistical analyses were performed using a personal computer with Stata/SE 16.1 for Windows (StataCorp LLC, Texas, USA).

Results

Patient characteristics

A total of 178 consecutive patients were admitted due to acute decompensated HF during the study period. Eighty-three patients (46.6%) had a high sBP of >140 mmHg on admission (CS1 group). In the non-CS1 group, 84 patients (48.0%) had sBP between 100 and 140 mmHg, and 11 patients (6.3%) had sBP less than 100 mmHg. All patients were underwent BIA on admission and before discharge. The characteristics of the patients are summarized in *Table 1*. The mean age of the patients was 79.5 years, and 48.9% of the patients were female. The mean left ventricular ejection fraction (LVEF) was 46.2%, and 48% of the patients had LVEF greater than 50%. Sixty-nine patients (38.8%) had a history of admission due to HF. There was no significant difference in age, weight, and LVEF between two groups. Hypertension was higher in CS1 group than in non-CS1 group, and pre-hospital diuretics use was lower in CS1 group than in non-CS1 group. One patient (1.2%) in CS1 group and one patient (1.1%) in non-CS1 group required intubation. A rate of using non-invasive positive pressure ventilation was significantly higher in CS1 group than in non-CS1 group (CS1 group: 26 patients, 31.3%, non-CS1 group; 10 patients, 10.5%, $P = 0.001$). Intravenous administration of furosemide (CS1 group; 71 patients, 85.5%, non-CS1 group; 58 patients, 61.1%, $P < 0.001$) and vasodilators (CS1 group; 83 patients, 46.6%, non-CS1 group; 32 patients, 33.7%, $P < 0.001$) were more frequently used in the CS1 group

Table 1 Clinical characteristics

	Overall	>140 (CS1) (*n* = 83)	≤140 (non-CS1) (*n* = 95)	*P* value
Female, *n* (%)	87 (48.9)	39 (47.0)	48 (50.5)	0.638
Age, years	79.5 ± 11.1	80.1 ± 11.6	78.9 ± 10.7	0.478
Weight, kg	52.4 ± 13.5	54.4 ± 15.0	50.6 ± 11.7	0.061
Body mass index, kg/m^2	21.1 ± 4.0	21.7 ± 4.4	20.7 ± 3.6	0.092
Hypertension, *n* (%)	128 (71.9)	68 (81.9)	60 (63.2)	0.005*
Diabetes mellitus, *n* (%)	63 (35.4)	32 (38.6)	31 (32.6)	0.410
Dyslipidaemia, *n* (%)	63 (35.4)	29 (34.9)	34 (35.8)	0.906
Current smoking, *n* (%)	21 (11.8)	16 (19.3)	5 (5.3)	0.004*
Prior myocardial infarction, *n* (%)	35 (19.7)	16 (19.3)	19 (20.0)	0.904
Chronic kidney disease, *n* (%)	82 (46.7)	42 (50.6)	40 (42.1)	0.257
AF or AT, *n* (%)	81 (45.5)	33 (39.8)	48 (50.5)	0.150
History of admission due to HF, *n* (%)	69 (38.8)	26 (31.3)	43 (45.3)	0.057
ACEI or ARB, *n* (%)	93 (52.2)	43 (51.8)	50 (52.6)	0.913
Beta-blocker, *n* (%)	81 (45.5)	32 (38.6)	49 (51.6)	0.082
Diuretics, *n* (%)	97 (54.5)	37 (44.6)	60 (63.2)	0.013*
LVEF, %	46.2 ± 16.2	47.2 ± 15.1	45.3 ± 17.1	0.428
LVEF ≥50%, *n* (%)	85 (47.8)	40 (48.2)	45 (47.4)	0.913
LVEF <40%, *n* (%)	65 (36.5)	29 (34.9)	36 (37.9)	0.683
Dilated cardiomyopathy, *n* (%)	16 (9)	5 (6)	11 (11.6)	0.196
Ischaemic heart disease, *n* (%)	46 (25.8)	22 (26.5)	24 (25.3)	0.850

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; AT, atrial tachycardia; CS1, clinical scenario 1; HF, heart failure; LVEF, left ventricular ejection fraction.
Data are expressed as number (%) or mean ± standard deviation.
*Values of $P < 0.05$ were considered to be significant.

patients, and inotropic agents were used more frequently in the non-CS1 group (CS1 group; 7 patients, 8.4%, non-CS1 patients; 19 patients, 20.0%, $P = 0.029$) (*Table 2*). The use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and beta-blocker was low at admission (*Table 1*), but increased at discharge (*Table 2*). The rate of use did not differ between the CS-1 and non-CS1 groups throughout the study. No patients received sacubitril/valsartan.

Changes in EI from the acute phase to the stable phase

EI and weight were evaluated in all 178 patients on admission (acute phase) and before discharge (stable phase). TRPG was evaluated in both the acute and stable phases in 139 patients: diameter of IVCinsp was measured in both phases in 131 patients, and LogNT-proBNP was measured in both phases in 146 patients. EI, weight, diameter of IVCinsp, TRPG, and LogNT-proBNP all significantly decreased from the acute phase to the stable phase in all patients with HF (0.413 ± 0.018 vs. 0.408 ± 0.013, $P < 0.001$; 56.3 ± 15.4 vs. 52.4 ± 13.5 kg, $P < 0.001$; 9.3 ± 5.2 vs. 6.6 ± 3.4 mm, $P < 0.001$; 42.6 ± 15.2 vs. 33.9 ± 11.9 mmHg, $P < 0.001$; 3.69 ± 0.50 vs. 3.30 ± 0.51, $P < 0.001$, respectively) (*Figure 1A–E*).

Comparisons between CS1 group and non-CS1 group

Table 3 shows comparisons of parameters between the two groups in the acute phase and stable phase. In both phases, diameter of IVCinsp was significantly larger in non-CS1 group than in CS1 group, and stroke volume was significantly larger in CS1 group than in non-CS1 group. Weight, LogNT-proBNP, LVEF, and left ventricular diastolic function assessed by E/A ratio and E/e' ratio were not significantly different between the two groups. In acute phase, TRPG was not significantly different between the two groups.

Acute phase EI in CS1 group was lower than that in non-CS1 group (0.409 ± 0.017 vs. 0.416 ± 0.019, $P = 0.008$). However, there was no significant difference in EI in the stable phase between the two groups (0.407 ± 0.015 vs. 0.410 ± 0.012, $P = 0.153$) (*Figure 2*). The change in EI from the acute phase to stable phase was no significant in CS1 group (0.409 ± 0.017 vs. 0.407 ± 0.015, $P = 0.176$) but was significant in non-CS1 group (0.416 ± 0.019 vs. 0.410 ± 0.012, $P < 0.001$) (*Figure 2*).

Table 4 was demonstrated comparisons of changes from acute to stable phase between CS1 group and non-CS1 group. The delta TRPG, delta IVCinsp, delta LogNT-proBNP, and delta weight were not significantly difference between the two groups. In BIA data, CS1 group had significantly smaller delta EI, delta TBW, delta ICW, and delta ECW than non-CS1 group.

Association between high EI and cardiac events

During the 1-year follow-up period after discharge of the 178 patients, 23 patients (12.9%) had incomplete 1-year follow-up. The numbers of deaths and re-admissions due to acute HF were 26 (15%) and 49 (28%), respectively. The median EI before discharge (in the stable phase) was 0.408 in all of the patients, and EI higher than the median at discharge was associated with a high incidence of all-cause death or re-admission due to AHF within 1 year after discharge [hazard ratio (HR): 2.15, 95% confidence interval (CI): 1.30–3.55, $P = 0.003$] (*Figure 3*).

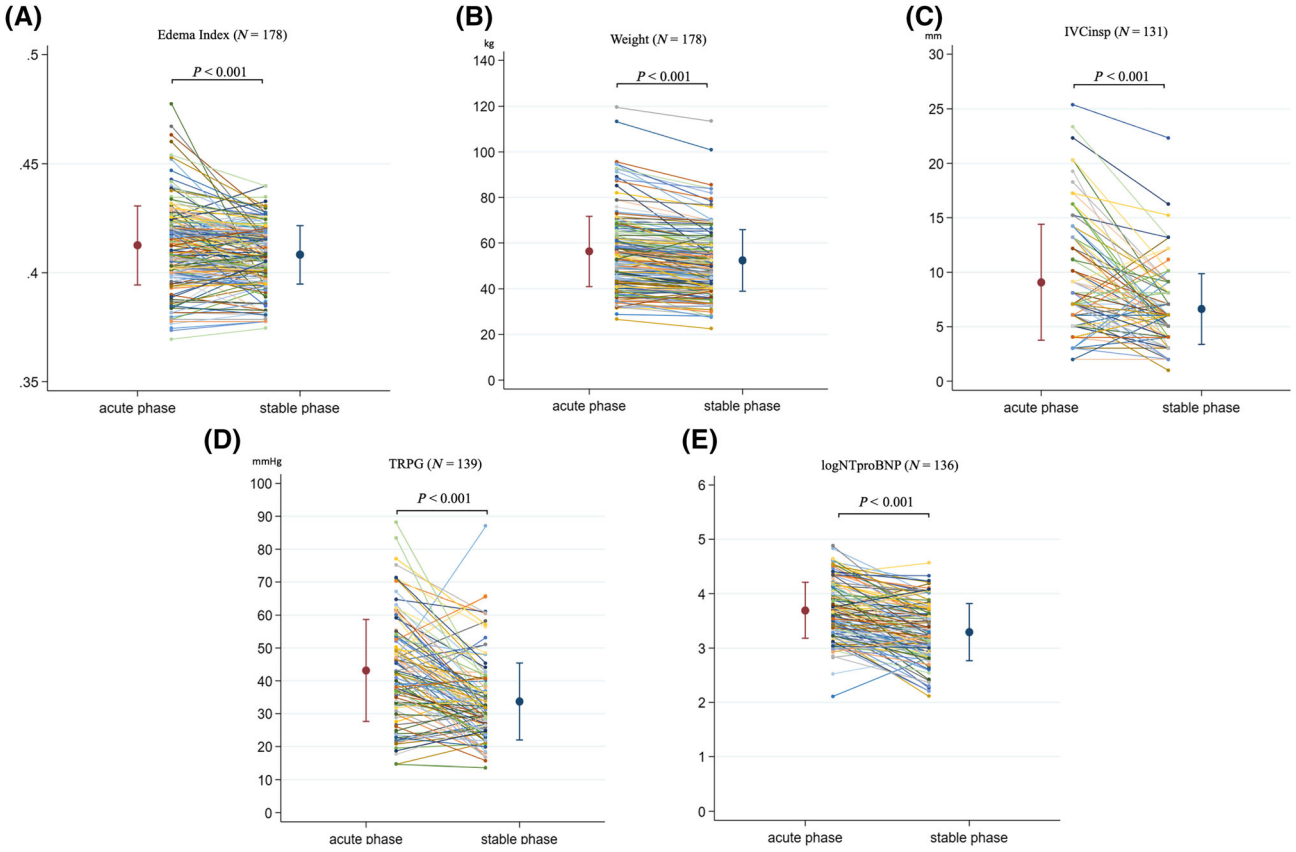
Cox regression analysis for composite outcome revealed that an increase of 0.01 in EI at stable phase increased a risk of all-cause death or re-admission due to HF within 1 year after discharge by a factor of 1.39 (95% CI: 1.15–1.68, $P < 0.001$) (*Table 5*). Age, TRPG, IVC, serum albumin, LogNT-proBNP, and weight were also associated with composite outcome. Higher EI as a continuous variable was significantly associated with worse outcome in non-CS1 group (HR: 1.46, 95% CI: 1.13–1.87, $P = 0.003$), but not significantly associated with worse outcome in CS1 group (HR: 1.29, 95% CI: 0.98–1.69, $P = 0.074$). In CS1 group, higher LogNT-proBNP

Table 2 Acute treatment and internal medicine at discharge

	Overall	>140 (CS1) ($n = 83$)	≤140 (non-CS1) ($n = 95$)	*P* value
NPPV, *n* (%)	36 (20.2)	26 (31.3)	10 (10.5)	0.001*
Intubation, *n* (%)	2 (1.1)	1 (1.2)	1 (1.1)	0.923
Intravenous furosemide	129 (72.5)	71 (85.5)	58 (61.1)	< 0.001*
Vasodilators	83 (46.6)	51 (61.5)	32 (33.7)	< 0.001*
Inotropic agents	26 (14.6)	7 (8.4)	19 (20.0)	0.029*
Internal medicine at discharge				
ACEI/ARB	134 (75.3)	66 (79.5)	68 (71.6)	0.221
Beta-blocker	139 (78.1)	68 (81.9)	71 (74.7)	0.247
Loop diuretics	150 (84.3)	76 (91.6)	84 (88.4)	0.487
Tolvaptan	71 (39.9)	23 (27.7)	48 (50.5)	0.002*

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CS1, clinical scenario 1; NPPV, non-invasive positive pressure ventilation.
*Values of $P < 0.05$ were considered to be significant.

Figure 1 Changes in oedema index and conventional parameters from the acute phase to the stable phase. The figures show changes from the acute phase to the stable phase in oedema index (A) and other heart failure parameters [(B) weight, (C) diameter of inferior vena cava during inspiration (IVCinsp), (D) tricuspid regurgitation pressure gradient (TRPG), (E) log transformation of *N*-terminal prohormone of brain natriuretic peptide (LogNT-proBNP)]. Oedema index significantly decreased from the acute phase to the stable phase as did other parameters. Data are expressed as means ± standard deviation.



and higher weight were significantly associated with worse outcome.

The event rates of death or re-admission due to heart failure at 1-year follow-up were similar in patients with preserved LVEF (LVEF ≥50%) and those with reduced LVEF (HR: 0.98, 95% CI: 0.61–1.59, *P* = 0.927).

Worsening renal function with treatment, defined as a 0.3 mg/dL increase in serum creatinine, was observed in 25 (30.1%) patients in the CS1 group and 20 patients (21.1%) in the non-CS1 group (*P* = 0.615).

Discussion

The present study demonstrated that EI obtained by using BIA was significantly related to interstitial congestion and that higher EI before discharge was significantly associated with worse outcomes including all-cause death and HF-related re-admission at 1 year in HF patients without high sBP on admission but not in patients with high sBP on admission.

The principal goal of treatment for HF is to remove excess body fluid, generally through the use of diuretics.[16] The conventional parameters of HF status, that is, NT-proBNP, TRPG, IVC diameter, and weight, should decrease as HF status improves. These parameters were reduced in the stable phase compared with those in the acute phase in this study. BIA-measured EI was also reduced in the stable phase compared with that in the acute phase. Previous studies showed that BIA is useful for estimating the state of HF and predicting outcome in patients with HF.[17–19] Weight data are necessary for calculating ECW, ICW, and TBW in BIA. However, the influence of weight is small because EI is a ratio. Although weight is a good indicator of HF treatment progress, some patients with AHF cannot be weighed due to dyspnoea or muscle weakness of the legs. BIA can be performed while lying or seated, and therefore, patients who are not able to stand can still be assessed by BIA.

Table 3 Comparisons of parameters between two groups in the acute phase and stable phase

	Acute phase					Stable phase				
	>140 (CS1) group		≤140 (non-CS1) group			>140 (CS1) group		≤140 (non-CS1) group		
	n	Mean	*n*	Mean	*P* value	*n*	Mean	*n*	Mean	*P* value
Weight	83	57.6 ± 16.8	95	55.2 ± 14	0.289	83	54.4 ± 15	95	50.6 ± 11.7	0.062
LogNT-proBNP	71	3.66 ± 0.51	81	3.73 ± 0.51	0.426	78	3.22 ± 0.54	90	3.36 ± 0.51	0.086
TTE date										
LAD	79	46 ± 5.6	91	47 ± 8.6	0.285	59	45 ± 6.8	69	47 ± 7.2	0.191
LVDd	80	52 ± 8.4	92	50 ± 8.9	0.234	68	50 ± 7.7	81	49 ± 8.7	0.451
LVDs	80	40 ± 10.9	92	39 ± 11.7	0.593	68	37 ± 9.6	81	38 ± 11.5	0.917
LVEF	80	44 ± 16.5	91	42 ± 17.7	0.532	68	48 ± 14.1	82	45 ± 17.3	0.190
Stroke volume	81	54 ± 18	92	49 ± 16.4	0.038*	69	57 ± 15.8	81	49 ± 13.2	0.001*
Cardiac output	81	4.0 ± 1.2	91	4.1 ± 1.5	0.509	69	3.7 ± 1.1	81	3.5 ± 1.1	0.331
Cardiac index	81	2.6 ± 0.8	91	2.8 ± 1.1	0.166	69	2.4 ± 0.8	81	2.4 ± 0.8	0.929
TRPG	77	41 ± 14.6	90	45 ± 16.1	0.068	68	31 ± 8.3	82	36 ± 13.6	0.018*
IVCinsp	73	7.4 ± 4.2	88	10.4 ± 5.8	<0.001*	66	6.0 ± 2.4	82	7.1 ± 3.7	0.030*
E/A ratio	47	1.2 ± 0.7	42	1.5 ± 0.9	0.100	46	1.0 ± 0.7	48	1.2 ± 0.9	0.221
E/e' ratio	72	20 ± 9.3	70	22 ± 9.4	0.317	64	18 ± 5.5	69	20 ± 7.7	0.185
BIA data										
Oedema index	83	0.409 ± 0.017	95	0.416 ± 0.019	0.008*	83	0.407 ± 0.015	95	0.410 ± 0.012	0.153
TBW	83	30.9 ± 8.8	95	30.7 ± 8.4	0.898	83	28.6 ± 7.8	95	27 ± 6.7	0.151
ICW	83	18.3 ± 5.3	95	17.9 ± 4.7	0.604	83	17.0 ± 4.9	95	16.0 ± 4.0	0.115
ECW	83	12.6 ± 3.6	95	12.8 ± 3.9	0.693	83	11.6 ± 3.0	95	11.1 ± 2.8	0.231
Protein	83	7.9 ± 2.3	95	7.7 ± 2.0	0.633	83	7.4 ± 2.1	95	6.9 ± 1.7	0.109
Mineral	83	2.9 ± 0.7	95	2.9 ± 0.6	0.841	83	2.7 ± 0.6	95	2.6 ± 0.5	0.389
Body fat mass	83	15.9 ± 9.4	95	13.8 ± 7.8	0.098	83	15.8 ± 8.3	95	14.1 ± 6.9	0.146
Soft lean mass	83	39.3 ± 11.2	95	39 ± 10.6	0.837	83	36.4 ± 10.1	95	34.4 ± 8.6	0.142

BIA, bioelectrical impedance analysis; CS1, clinical scenario 1; ECW, extracellular water; EI, oedema index; ICW, intracellular water; IVCinsp, inferior vena cava during inspiration; LAD, left atrial dimension; LogNT-proBNP, log transformation of *N*-terminal pro-brain natriuretic peptide; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic dimeter, LVEF, left ventricular ejection fraction; TBW, total body water; TRPG, tricuspid regurgitation pressure gradient; TTE, transthoracic echocardiography.
Data are expressed as number or mean ± standard deviation.
*Values of $P < 0.05$ were considered to be significant.

Figure 2 Comparison of oedema indexes in the sBP > 140 (CS1) and sBP ≤ 140 (non-CS1) groups. Oedema index in the acute phase was significantly higher in the sBP ≤ 140 (non-CS1) group than in the sBP > 140 (CS1) group, and oedema index was decreased significantly by treatment for heart failure. On the other hand, in CS1 group, there was no significant difference in the oedema indexes before and after treatment for heart failure. Data are expressed as means ± standard deviation.

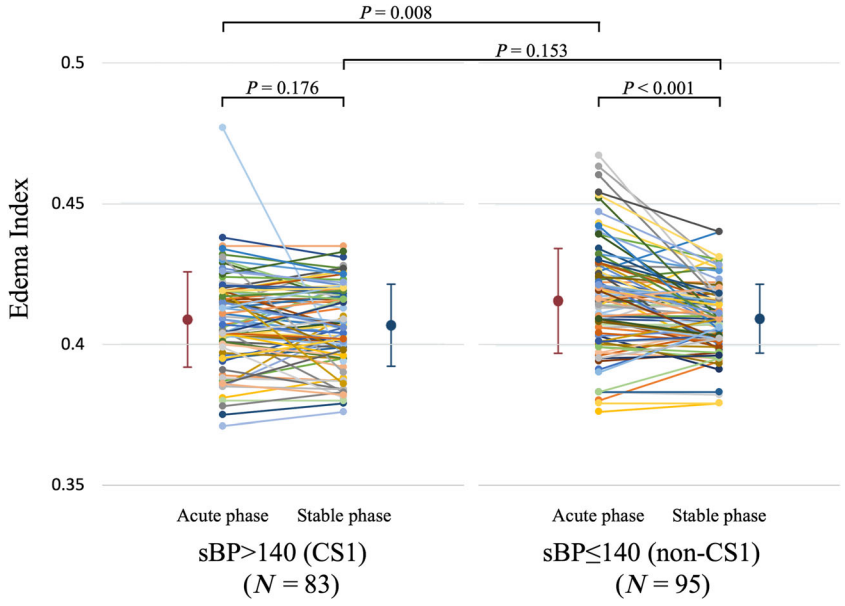
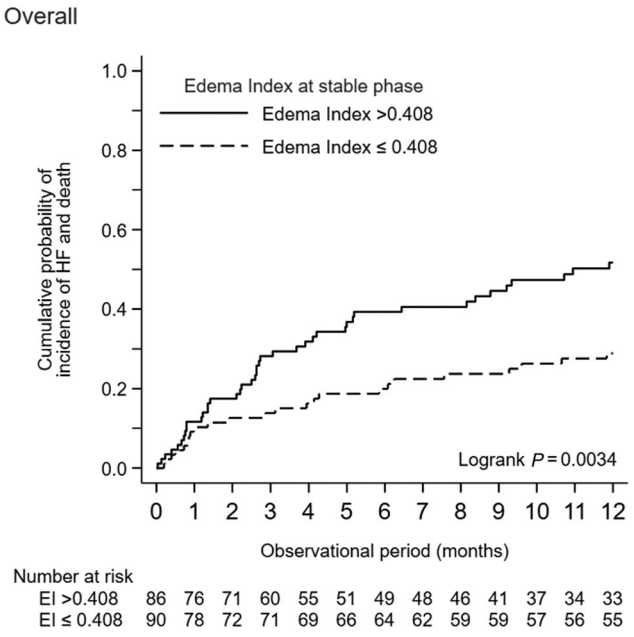


Table 4 Comparisons of changes from acute to stable phase between CS1 group and non-CS1 group

	CS 1	non-CS1	*P* value
delta TRPG	9.08 ± 13.29	8.56 ± 15.47	0.8344
delta IVC	1.96 ± 4.32	3.21 ± 4.79	0.126
delta LogNT-proBNP	0.41 ± 0.46	0.37 ± 0.41	0.5911
delta Body weight	3.23 ± 4.39	4.55 ± 5.84	0.0931
BIA Data			
delta Oedema index	0.0020 ± 0.0135	0.0063 ± 0.0131	0.0331
delta Total body water	2.3 ± 3.28	3.71 ± 3.65	0.0077
delta Intracellular water	1.27 ± 1.74	1.93 ± 1.77	0.0125
delta Extracellular water	1.03 ± 1.66	1.78 ± 1.95	0.0071

BIA, bioelectrical impedance analysis; IVCinsp, inferior vena cava during inspiration; LogNT-proBNP, log transformation of *N*-terminal pro-brain natriuretic peptide; TRPG, tricuspid regurgitation pressure gradient.

Figure 3 Kaplan–Meier curves for composite cardiac events in overall patients and patients in the two groups. The median oedema indexes before discharge (in the stable phase) were 0.408 in overall patients. The figures show Kaplan–Meier curves for composite cardiac events including all-cause death and heart failure-related rehospitalization in overall patients. Patients with oedema index higher than the median had a significantly higher incidence of cardiac events at 1 year after discharge.



AHF is categorized by sBP, and sBP > 140 mmHg is hypertensive AHF.[4] Some studies have suggested that hypertensive HF is caused by fluid redistribution, not interstitial congestion.[5] For such patients, diuretics are not absolutely necessary for treatment of HF.[2] In the present study, changes in conventional parameters from acute phase to stable phase were not significantly difference between the CS1 and non-CS1 group. It is difficult to distinguish AHF with interstitial congestion or intravascular congestion by conventional parameter. However, our study showed that changes in EI, TBW, ICW, and ECW were significantly smaller in the CS1 group than in the non-CS1 group. The EI measured by BIA may be useful to diagnose the AHF phenotype. Then, in non-CS1 group, higher EI before discharge was significantly associated with higher incidences of all-cause death and HF-related re-admission at 1-year. Mebazaa *et al*. recommend treatment with non-invasive ventilation and nitrates in patients with CS1. Diuretics are rarely indicated unless volume overload is present.[6] This study confirms that their recommended treatment is appropriate. Because the need for diuretics for AHF is determined by the phenotype of AHF, EI measured by BIA can be meaningful data for determining the use of diuretics for AHF. Further studies are needed to clarify this point.

Study limitations

Some potential limitations of the present study must be considered. First, we did not set a specific timing to perform BIA. There are diurnal variations in data obtained by BIA, and BIA data are also influenced by meals, excretion, and exercise. It is difficult to perform BIA at the same time every day in clinical practice, and our study was conducted in this setting. Second, echocardiography, BIA, and blood sampling were not performed at the same time. If the aim of this study was to estimate TRPG or NT-proBNP from EI, these measurements should be performed at the same time. However, this study was performed to assess the trend of EI in treatment of HF. Third, we were unable to obtain sufficient right heart catheter data. This was a prospective observational study, and not all patients underwent right heart catheterization. In addition, the BIA has a device that can calculate cardiac index, but the InBodyS10® could not calculate cardiac index. Further studies are needed to clarify the relationship between EI and right heart catheter data or cardiac index by BIA. Fourth, acute EI could be falsified by initial treatment because acute testing was performed within 7 days of admission in this study. However, most patients were performed BIA within 3 days of admission (CS1: 73 out of 83, 88% vs. non-CS1: 87 out of 95, 92%; *P* = 0.423), and acute-phase EI in CS1 group was significantly lower than those in non-CS1 group (0.408 ± 0.015 vs. 0.416 ± 0.019, *P* = 0.002), and delta EI was smaller in CS1 group than in non-CS1 group

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Table 5 Cox regression analysis for composite outcome

	Overall			>140 group (CS1)			≤140 group		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.02	1.00–1.05	0.049	1.02	0.99–1.06	0.257	1.03	1.00–1.06	0.098
Male	0.97	0.60–1.57	0.896	0.66	0.31–1.40	0.279	1.32	0.70–2.48	0.385
LVEF	1.00	0.98–1.01	0.768	1.00	0.98–1.03	0.847	1.00	0.98–1.01	0.605
TRPG	1.03	1.01–1.05	0.003	1.04	0.99–1.10	0.149	1.03	1.00–1.05	0.017
IVCinsp	1.08	1.01–1.16	0.020	1.07	0.88–1.31	0.485	1.08	1.00–1.16	0.049
Serum albumin	0.57	0.36–0.90	0.015	0.59	0.28–1.24	0.162	0.58	0.32–1.05	0.071
LogNT-proBNP	2.14	1.37–3.35	0.001	1.99	0.98–4.05	0.056	2.2	1.22–3.97	0.009
Oedema index	1.39	1.15–1.68	0.001	1.29	0.98–1.69	0.074	1.46	1.13–1.87	0.003
Weight	0.98	0.96–1.00	0.018	0.97	0.95–1.00	0.079	0.98	0.95–1.01	0.131
Total body water	0.97	0.94–1.01	0.142	0.96	0.91–1.01	0.137	0.99	0.94–1.04	0.639
Intracellular water	0.95	0.90–1.01	0.079	0.93	0.86–1.02	0.114	0.97	0.89–1.05	0.446
Extracellular water	0.96	0.88–1.04	0.319	0.92	0.80–1.04	0.192	1.00	0.89–1.12	0.979
Protein	0.89	0.78–1.02	0.084	0.86	0.70–1.04	0.120	0.93	0.77–1.12	0.455
Minerals	0.74	0.46–1.17	0.194	0.52	0.24–1.10	0.087	0.98	0.54–1.79	0.952
Body fat mass	0.96	0.92–0.99	0.020	0.97	0.92–1.02	0.179	0.95	0.90–1.00	0.053
Soft lean mass	0.98	0.95–1.01	0.128	0.97	0.93–1.01	0.133	0.99	0.95–1.03	0.601
Lean mass index	0.93	0.83–1.05	0.227	0.89	0.74–1.07	0.202	0.97	0.83–1.13	0.722

CS1, clinical scenario 1; EI, oedema index; IVCinsp, inferior vena cava during inspiration; LogNT-proBNP, log transformation of *N*-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction, TRPG, tricuspid regurgitation pressure gradient.

(0.0018 ± 0.0101 vs. 0.0066 ± 0.0133, $P = 0.012$). Fifth, we did not evaluate troponin as a prognostic and injury marker. Finally, this is a single-centre study, and we had many missing data despite the prospective study design.

Conclusions

EI on admission in patients with sBP > 140 mmHg was not elevated, and changes in ECW, ICW, TBW, and EI in patients with sBP > 140 mmHg were smaller than those in patients with sBP of ≤140 mmHg. EI measured by BIA could distinguish AHF with interstitial or intravascular congestion.

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Conflict of interest

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