Association between intestinal oedema and oral loop diuretic resistance in hospitalized patients with acute heart failure

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Abstract

Aims Intestinal oedema is one of the manifestations associated with right-sided heart failure (HF), which is known to be associated with poorer patient outcomes. We attempted to reveal the association between intestinal oedema and diuretic resistance in hospitalized patients with acute HF.

Methods and results Among 213 hospitalized patients with acute HF, abdominal ultrasonography was performed under clinically stable conditions after initial HF treatments. The association among abdominal ultrasonographic parameters, maintenance doses of loop diuretics, and responsiveness to initial loop diuretic treatment was evaluated. Higher mean colon wall thickness (CWT) independently correlated with a higher dose of loop diuretics at enrolment (adjusted β = 0.198, P = 0.0004). Increased mean CWT also correlated with poor response to oral loop diuretics as an initial treatment, whereas it did not correlate with the response to intravenous loop diuretics. Discrimination of non-responders to initial oral loop diuretics resulted in a sensitivity of 0.772 and a specificity of 0.733 using a mean CWT cut-off value of ≥3 mm.

Conclusions In hospitalized patients with acute HF, a strong correlation was identified among the severity of intestinal oedema, required quantities as maintenance loop diuretic doses, and poor responsiveness to oral loop diuretics at admission.

Keywords Intestine; Heart failure; Diuretic; Outcome

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Introduction

Congestion is one of the most major pathophysiological conditions in patients with heart failure (HF). Systemic congestion including multiple organs reduces the quality of life of patients with HF and also results in poorer long-term prognosis. Diuretics have been generally used to relieve congestion in HF treatment. Moreover, the term “diuretic resistance” is widely known, which can be explained as a failure of diuretics to control salt and water retention even when used in appropriate doses. Studies have also reported that patients with HF with diuretic resistance have higher occurrence of clinical events of HF deterioration and higher mortality.

Loop diuretics have been most widely used as decongestive agents in HF treatment. They inhibit the Na+/2Cl−/K+ cotransporter of the thick ascending loop of Henle, resulting in decreased sodium and chloride reabsorption from the urine and subsequent natriuresis. The two routes of administration of loop diuretics are as follows: oral and intravenous. In general, intravenous administration is applied in hospitalized patients during the acute phase, and oral administration is applied during the subacute or chronic phase.

It is well established that patients with chronic HF have intestinal oedema. Intestinal oedema has been interpreted as one of the manifestations associated with right-sided HF accompanied by increased central venous pressure. It has been specifically reported that intestinal oedema manifests...
in the advanced stage of HF and is believed to be involved in the vicious cycle of HF.\textsuperscript{10–12} It is assumed that intestinal oedema in HF, in particular in acute decompensated settings, might reduce the bioavailability of orally administrated loop diuretics. Therefore, intravenous administration of loop diuretics during the initial HF treatment, instead of oral administration, should maximize the efficacy of the administered loop diuretics in patients with intestinal oedema. Optimal selection of the administration route of loop diuretics might reduce the poor diuretic responsiveness in patients undergoing acute HF treatment.

In the present study, we attempted to disclose the association between intestinal oedema and diuretic resistance in hospitalized patients with acute HF and then explore whether the administration route of loop diuretics were related to the poor diuretic responsiveness in patients with intestinal oedema.

**Methods**

**Study population**

This research was a single-centre, prospective, and observational study conducted on Japanese patients with HF and was approved by the ethics committee of Kitasato University Hospital. Patient recruitment was conducted from February 1, 2015 to August 31, 2016. Eligibility criteria were as follows: (i) hospitalized patients with acute HF corresponding to the Framingham classification\textsuperscript{13}; (ii) age $>$ 20 years; and (iii) availability of information regarding urine volume, body weight, and medications. The exclusion criteria were patients who did not wish to participate in the study; those with acute coronary syndrome within the past 3 months; and patients with active gastrointestinal disease, including gastrointestinal cancer, any cause of enteritis/colitis, inflammatory bowel disease, food hypersensitivity, and ileus. All patients received optimal HF treatments during the hospitalization period according to current HF guidelines.\textsuperscript{14}

**Study protocol**

Details regarding the demographics, medications, physical examination, blood sampling parameters, echocardiographic parameters, and abdominal ultrasonographic parameters of the patients were obtained under clinically stable conditions after initial HF treatments. To elucidate the diuretic response, the changes in urine volume and body weight after initial loop diuretic treatment at admission (per 48 h/40 mg of furosemide-equivalent) were evaluated.\textsuperscript{5,15} Non-responders to initial loop diuretic treatment were defined on the basis of the following criterion: change in urine volume $< +1000$ mL/48 h/40 mg of furosemide or $\geq +0$ kg/48 h/40 mg of furosemide. Assuming that 40 mg of oral furosemide was equivalent to 20 mg of intravenous furosemide, the dose of furosemide was presented as oral furosemide-equivalent. Patients were followed up for the evaluation of adverse events for a maximum period of 18 months after baseline assessment.

**Ultrasonographic measurements**

Echocardiography was performed transthoracically and repeated by the same experienced ultrasonographers whenever possible according to the recommendation of the American Society of Echocardiography.\textsuperscript{16} Abdominal ultrasonographic parameters were obtained to evaluate blood flow parameters and intestinal wall thickness by one experienced ultrasonographer and reviewed by another ultrasonographer independent of the patient’s clinical information. All abdominal ultrasonographic parameters were evaluated using similar methods as performed in our previous report.\textsuperscript{13} Intestinal blood flow parameters, including the cross-sectional area (CSA), maximum velocity, blood flow volume, pulsatility index (PI) [$= (\text{maximum velocity – minimum velocity})/\text{mean velocity}$], and congestion index (CI, only at the portal vein (PV)) [$= \text{CSA}/\text{mean velocity}$], were evaluated at the superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and PV. Intestinal wall thickness was evaluated at the ascending, transverse, descending, and sigmoid colon. Mean colon wall thickness (CWT) was calculated according to the following formula: mean CWT = (ascending + transverse + descending + sigmoid CWT)/4. Representative images to evaluate PV blood flow parameters and colon wall thickness are presented in Supporting Information, Figure S1.

**Adverse events**

Patients were followed up for the observation of (i) composite events, including the first occurrence of readmission for deteriorated HF, major ventricular arrhythmias (ventricular fibrillation and sustained ventricular tachycardia), or all-cause mortality, and (ii) the occurrence of all-cause mortality.

**Statistical analysis**

Data are presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. For comparison between groups, Student’s $t$-test or the Wilcoxon rank sum test was used for continuous variables, and the $\chi^2$ test or Fisher’s exact test was used for categorical variables. To clarify the relationships between clinical parameters and dose of loop diuretics, multiple regression models were used, and the $\beta$ coefficients were calculated. Factors with $P < 0.05$ in univariate regression...
analyses were identified as candidate predictive factors for multivariate analysis; predictive factors were identified in the multivariate analysis by backward stepwise selection ($P < 0.05$). Same covariates for predictive of dose of loop diuretics were included in multivariate analyses for determining the association with non-responders to initial loop diuretic treatment after dividing the patients based on the administration of either oral or intravenous loop diuretic treatment. The Kaplan–Meier method was used to draw the stratified event-free rates. A receiver operating characteristic curve was constructed to determine the accuracy of the prediction of non-responders to oral loop diuretics at admission using mean CWT and to detect the cut-off level. A $P$ value $< 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using JMP 13 (SAS Institute, Cary, NC, USA).

Results

Study patients

The study overview is depicted in Figure 1. A total of 213 patients were included in our study. At admission, 80% of patients were treated with loop diuretics (49% of patients were treated with intravenous loop diuretics, and 31% of patients were treated with oral loop diuretics). Primary data collection was done at a mean of 9 days after admission. At enrolment, 84% of patients were treated with loop diuretics, with a dose of 40–160 mg/day being used in 33% of patients.

Patient characteristics stratified according to the dose of loop diuretics

Patients were stratified into four groups based on the dose of loop diuretics at enrolment as presented in Table 1. Group 1 included patients with no loop diuretics, Group 2 included patients treated with 5–30 mg/day, Group 3 included patients treated with 40 mg/day, and Group 4 included those treated with 50–160 mg/day of loop diuretics. Regarding demographic characteristics, patients in Groups 3 and 4 were of higher age. Among medications, there was a higher rate of usage and doses of loop diuretics or other diuretics in groups treated with a higher dose of loop diuretics at enrolment. Intravenous inotropes were more frequently used in Groups 3 and 4. Groups treated with a higher dose of loop diuretics at enrolment had higher New York Heart Association class, lower systolic blood pressure, higher heart rate, higher presence of atrial fibrillation, and higher rate of introduced pacemaker devices. These groups also had lower serum albumin level, higher total bilirubin level, lower estimated glomerular filtration rate, lower serum sodium concentration, and higher B-type natrium peptide level. Moreover, poor left ventricular systolic/diastolic function, poor right ventricular...
### Table 1  Patient characteristics at enrolment

| Variable                     | All  \((n = 213)\) | Group 1: 0 mg/day \((n = 34)\) | Group 2: 5–30 mg/day \((n = 109)\) | Group 3: 40 mg/day \((n = 51)\) | Group 4: 50–160 mg/day \((n = 19)\) |
|------------------------------|------------------|-------------------------------|---------------------------------|---------------------------------|----------------------------------|
| **Demographic**              |                  |                               |                                 |                                 |                                  |
| Age (years)                  | 68 ± 13 (34)     | 64 ± 14 (34)                 | 68 ± 12 (109)                  | 71 ± 13* (51)                   | 70 ± 16* (19)                    |
| Gender, males, n (%)         | 125 (59)         | 21 (62)                      | 68 (62)                        | 25 (49)                         | 11 (58)                          |
| Ischemic aetiology, n (%)    | 78 (37)          | 18 (53)                      | 38 (35)                        | 17 (33)                         | 5 (26)                           |
| Hypertension, n (%)          | 118 (55)         | 22 (65)                      | 58 (53)                        | 30 (59)                         | 8 (42)                           |
| Diabetes, n (%)              | 86 (40)          | 12 (35)                      | 47 (43)                        | 23 (45)                         | 4 (21)                           |
| Body weight (kg)             | 59 ± 15 (34)     | 60 ± 12 (34)                 | 61 ± 18 (109)                  | 55 ± 13* (51)                   | 56 ± 7                           |
| **Medication**               |                  |                               |                                 |                                 |                                  |
| Beta-blockers, n (%)         | 175 (82)         | 24 (71)                      | 97 (89)*                       | 40 (78)                         | 14 (74)                          |
| ACEi or ARB, n (%)           | 192 (90)         | 27 (79)                      | 99 (91)                        | 49 (96)                         | 17 (89)                          |
| Loop diuretics at admission, n (%) | 46 (22)       | 5 (15)                       | 96 (88)*                       | 51 (100)*                       | 19 (100)*                        |
| **Dose of loop diuretics at admission (mg/day)** | 27 ± 20 (34)    | 3 ± 9                        | 26 ± 16*                       | 41 ± 14†                        | 45 ± 18†                         |
| **Dose of loop diuretics at enrolment (mg/day)** | 25 ± 21 (34)    | 0 ± 0                        | 18 ± 5*                        | 40 ± 0*†                        | 75 ± 23†                         |
| Aldosterone antagonists, n (%) | 115 (54)        | 7 (21)                       | 67 (61)*                       | 30 (59)*                        | 11 (58)*                         |
| Thiazides, n (%)             | 15 (7)           | 0 (0)                        | 2 (2)                          | 6 (12)*†                        | 7 (37)*†                         |
| Tolvaptan, n (%)             | 50 (23)          | 0 (0)                        | 22 (20)*                       | 11 (22)*                        | 9 (47)*†                         |
| **Clinical condition**       |                  |                               |                                 |                                 |                                  |
| NYHA IV, n (%)               | 31 (15)          | 0 (0)                        | 11 (10)*                       | 11 (22)*†                       | 9 (47)*†                         |
| Systolic blood pressure (mmHg) | 110 ± 19         | 113 ± 17                     | 110 ± 18                       | 113 ± 21                        | 100 ± 18†                        |
| Heart rate (beats/min)       | 72 ± 12          | 68 ± 11                      | 72 ± 12                        | 71 ± 9                          | 83 ± 16†                         |
| Atrial fibrillation, n (%)   | 52 (24)          | 2 (9)                        | 29 (27)*                       | 15 (29)*                        | 6 (32)*                          |
| PM or CRT, n (%)             | 37 (17)          | 3 (1)                        | 17 (16)*                       | 13 (25)*                        | 6 (32)*                          |
| Serum albumin (g/dL)         | 3.4 ± 0.6        | 3.7 ± 0.5                    | 3.4 ± 0.6*                     | 3.3 ± 0.6*                      | 3.3 ± 0.4*                       |
| Total bilirubin (mg/dL)      | 0.8 ± 0.5        | 0.7 ± 0.3                    | 0.8 ± 0.5                      | 0.8 ± 0.6                        | 1.0 ± 0.4†                       |
| Estimated GFR (mL/min/1.73 m²) | 46 ± 21          | 60 ± 21                      | 49 ± 20*                       | 36 ± 18†                        | 34 ± 15†                         |
| Serum sodium (mEq/L)         | 138 ± 4         | 138 ± 3                      | 138 ± 3                        | 138 ± 5                          | 134 ± 6†                         |
| Serum potassium (mEq/L)      | 4.3 ± 0.5        | 4.3 ± 0.4                    | 4.3 ± 0.5                      | 4.4 ± 0.6                        | 4.1 ± 0.5                        |
| BNP (pg/mL)                  | 633 ± 792       | 211 ± 222                    | 591 ± 653*                     | 757 ± 754*                      | 1297 ± 1515†                     |
| **Echocardiography**         |                  |                               |                                 |                                 |                                  |
| LVEF (%)                     | 41 ± 18          | 50 ± 14                      | 38 ± 17*                       | 42 ± 19*                        | 37 ± 23*                         |
| LVEDD (mm)                   | 57 ± 13          | 49 ± 10                      | 59 ± 13*                       | 58 ± 14*                        | 56 ± 14*                         |
| LAD (mm)                     | 47 ± 10          | 40 ± 8                       | 47 ± 10*                       | 49 ± 9*                         | 49 ± 10*                         |
| RVEDD (mm)                   | 35 ± 9           | 30 ± 5                       | 35 ± 9*                        | 38 ± 10†                        | 39 ± 8†                          |
| TAPSE (mm)                   | 19 ± 5           | 22 ± 5                       | 19 ± 5*                        | 17 ± 5*                          | 14 ± 4†                           |
| SV (mL)                      | 50 ± 25          | 58 ± 22                      | 52 ± 29                        | 46 ± 21*                        | 36 ± 11†                          |
| E/E ratio                    | 19 ± 10          | 12 ± 7                       | 20 ± 10*                       | 19 ± 7*                          | 28 ± 17†                         |
| IVC dimension (mm)           | 18 ± 7           | 14 ± 5                       | 18 ± 6*                        | 21 ± 8†                          | 23 ± 5†                           |
| Moderate to severe MR, n (%) | 73 (34)          | 3 (9)                        | 36 (33)*                       | 26 (51)*†                        | 8 (42)*†                           |
| Moderate to severe TR, n (%) | 64 (30)          | 2 (6)                       | 29 (27)*                       | 23 (45)*†                        | 10 (53)*†                           |

Values are presented as mean ± standard deviation, or number of patients (%). 
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; E/E<sub>0</sub>, mitral E/average E<sub>0</sub>, GFR, glomerular filtration rate; IVC, inferior vena cava, LAD, left atrial dimension; LV<sub>ED</sub>D, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association class, PM, pacemaker; RV<sub>ED</sub>D, right ventricular end-diastolic dimension; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

*<i>P < 0.05, compared with Group 1.</i>
†<i>P < 0.05, compared with Group 2.</i>
systolic function, lower stroke volume, and higher presence of significant valvular diseases were observed in these groups.

Blood flow parameters at the SMA/IMA/PV and CWT at the ascending colon/transverse colon/descending colon/sigmoid colon are summarized in Table 2. No significant difference was observed in blood flow parameters at the SMA/IMA among the study groups. Groups treated with a higher dose of loop diuretics at enrolment had lower CSA, higher PI, and higher CI. These groups had higher CWT at any colon site and higher mean CWT.

Clinical factors associated with the dose of loop diuretics

Among the blood flow parameters at the SMA/IMA/PV, PV-CSA (unadjusted $\beta = 0.159, P = 0.020$) and PV-Cl (unadjusted $\beta = 0.163, P = 0.017$) were significantly associated with mean CWT. PV-CSA (unadjusted $\beta = 0.266, P < 0.0001$), PV-PI (unadjusted $\beta = 0.232, P < 0.0001$), and PV-Cl (unadjusted $\beta = 0.189, P = 0.005$) were significantly associated with the dose of loop diuretics at enrolment. Results of univariate and multivariate analyses for the association with the dose of loop diuretics were summarized in Table 3. Mean CWT showed an independent positive association with the dose of loop diuretics at enrolment.

Association between diuretic response and intestinal wall thickness

We divided the study patients according to whether they were treated with oral (67 patients) or intravenous (104 patients) loop diuretics at admission. Distribution of the diuretic response and the prevalence of

### Table 2

| Variable | All ($n = 213$) | Group 1: 0 mg/day ($n = 34$) | Group 2: 5–30 mg/day ($n = 109$) | Group 3: 40 mg/day ($n = 51$) | Group 4: 50–160 mg/day ($n = 19$) |
|----------|-----------------|-----------------------------|---------------------------------|-----------------------------|---------------------------------|
| SMA CSA (cm$^2$) | 0.28 ± 0.11 | 0.25 ± 0.09 | 0.30 ± 0.12 | 0.27 ± 0.10 | 0.31 ± 0.09 |
| $V_{\text{max}}$ (cm/s) | 177 ± 69 | 185 ± 78 | 173 ± 67 | 189 ± 71 | 155 ± 62 |
| BFV (mL/min) | 975 ± 518 | 955 ± 449 | 1002 ± 567 | 951 ± 475 | 918 ± 475 |
| PI | 2.7 ± 1.0 | 2.5 ± 1.0 | 2.6 ± 0.9 | 2.7 ± 0.9 | 2.9 ± 1.2 |
| IMA CSA (cm$^2$) | 0.11 ± 0.08 | 0.12 ± 0.15 | 0.10 ± 0.05 | 0.12 ± 0.08 | 0.11 ± 0.04 |
| $V_{\text{max}}$ (cm/s) | 126 ± 63 | 134 ± 62 | 122 ± 54 | 114 ± 76 | 165 ± 78 |
| BFV (mL/min) | 236 ± 208 | 274 ± 255 | 210 ± 183 | 238 ± 235 | 322 ± 154 |
| PI | 3.4 ± 1.4 | 3.2 ± 1.3 | 3.6 ± 1.4 | 3.3 ± 1.5 | 3.0 ± 1.3 |
| PV CSA (cm$^2$) | 0.65 ± 0.26 | 0.55 ± 0.20 | 0.63 ± 0.24 | 0.73 ± 0.33* | 0.79 ± 0.25*† |
| $V_{\text{max}}$ (cm/s) | 33 ± 13 | 36 ± 13 | 31 ± 11 | 35 ± 17 | 29 ± 9 |
| BFV (mL/min) | 1019 ± 454 | 1070 ± 415 | 979 ± 424 | 1067 ± 553 | 1030 ± 398 |
| PI | 0.37 ± 0.39 | 0.27 ± 0.14 | 0.31 ± 0.24 | 0.49 ± 0.65 | 0.51 ± 0.36*† |
| CI (cm/s) | 0.039 ± 0.050 | 0.022 ± 0.011 | 0.037 ± 0.052* | 0.047 ± 0.055* | 0.060 ± 0.059*† |
| CWT Ascending colon (mm) | 2.6 ± 1.0 | 2.2 ± 0.7 | 2.6 ± 1.0 | 2.8 ± 1.1* | 3.1 ± 1.3* |
| Transverse colon (mm) | 2.6 ± 0.8 | 2.2 ± 0.6 | 2.5 ± 0.8* | 2.8 ± 0.8* | 2.9 ± 0.7*† |
| Descending colon (mm) | 2.6 ± 0.9 | 2.1 ± 0.5 | 2.6 ± 0.9* | 2.9 ± 0.9* | 3.2 ± 1.0*† |
| Sigmoid colon (mm) | 2.8 ± 1.0 | 2.4 ± 0.6 | 2.8 ± 1.0 | 3.0 ± 1.0* | 3.4 ± 1.1*† |
| Mean CWT (mm) | 2.7 ± 0.8 | 2.2 ± 0.4 | 2.6 ± 0.7* | 2.9 ± 0.8* | 3.2 ± 0.8*† |

Values are presented as mean ± standard deviation.

BFV, blood flow volume; CI, congestion index; CSA, cross sectional area; CWT, colon wall thickness; IMA, inferior mesenteric artery; PI, pulsatile index; PV, portal vein; SMA, superior mesenteric artery; $V_{\text{max}}$, maximum velocity.

* $P < 0.05$, compared with Group 1.
† $P < 0.05$, compared with Group 2.
non-responders stratified according to mean CWT are shown in Figure 2. In total, 14 patients with mean CWT ≤ 2.0 mm, 15 with mean CWT 2.1–2.5 mm, 15 with mean CWT 2.6–3.0 mm, and 23 with mean CWT ≥ 3.1 mm among the patients treated with oral loop diuretics at admission. There were 14 patients with mean CWT ≤ 2.0 mm, 32 with mean CWT 2.1–2.5 mm, 30 with mean CWT 2.6–3.0 mm, and 28 with mean CWT ≥ 3.1 mm among the patients treated with intravenous loop diuretics at admission. A higher mean CWT was strongly and independently associated with non-responders among patients treated with oral loop diuretics at admission, whereas it was not associated in patients treated with intravenous loop diuretics at admission, as shown in Table 4. The receiver operating characteristic curve revealed an optimal mean CWT cut-off value of ≥3.0 mm for the association with non-responders, as shown in Figure 3.

### Long-term clinical events

Patients were followed up during a mean period of 328 ± 132 (range = 4–422) days after admission for observation of adverse events. There were 73 (34%) composite events, including 66 (31%) readmissions for deteriorated HF, 5 (2%) major ventricular arrhythmias, 2 (1%) non-cardiac deaths, and 23 (11%) events of all-cause mortality. Event-free rates of

**Figure 2** Distribution of the diuretic response and the prevalence of non-responders stratified according to mean CWT. Patients were divided according to whether they were treated with oral (left) or intravenous (right) loop diuretics at admission. Comparisons with patients with mean CWT ≤ 2.0 mm: *P < 0.05. CWT, colon wall thickness.

### Table 4 Univariate and multivariate analyses for association with non-responder to initial loop diuretic treatment

| Variable | Oral loop diuretics | Intravenous loop diuretics |
|----------|---------------------|---------------------------|
|          | Unadjusted odds ratio | Adjusted odds ratio | P value | Unadjusted odds ratio | Adjusted odds ratio | P value |
| Estimated GFR, per +1 SD | 0.527 (0.280–0.992) | 0.03 | 0.568 (0.267–1.210) | 0.1 | 0.409 (0.220–0.761) | 0.001 | 0.459 (0.234–0.899) | 0.01 |
| BNP, per +1 SD | 1.230 (0.620–2.442) | 0.5 | 1.042 (0.465–2.338) | 0.9 | 1.416 (0.995–2.015) | 0.05 | 1.138 (0.779–1.661) | 0.5 |
| IVC dimension, per +1 SD | 1.262 (0.735–2.166) | 0.3 | 1.155 (0.625–2.144) | 0.6 | 1.263 (0.747–2.135) | 0.3 | 1.177 (0.666–2.080) | 0.5 |
| Mean CWT, per +1 SD | 2.792 (1.536–5.076) | <0.0001 | 2.762 (1.449–5.263) | 0.0003 | 1.211 (0.685–2.141) | 0.5 | 1.090 (0.592–2.006) | 0.7 |

BNP, B-type natriuretic peptide; CWT, colon wall thickness; GFR, glomerular filtration rate; IVC, inferior vena cava.

Covariates into multivariate analyses were adjusted by age, ischemic aetiology, body weight, tricuspid annular plane systolic excursion, mitral E/average E', moderate to severe mitral regurgitation, and moderate to severe tricuspid regurgitation.
adverse events were drawn stratified according to the dose of loop diuretics at enrolment, mean CWT, and response to initial loop diuretic treatment, as depicted in Figure 4. A higher dose of loop diuretics at enrolment, higher mean CWT, and non-responders to initial loop diuretic treatment were associated with lower event-free rates of readmission for deteriorated HF and all-cause mortality.

**Discussion**

**Major findings**

The key findings of the present study can be summarized as follows: (i) a higher mean CWT independently correlated with a higher maintenance dose of loop diuretics in patients hospitalized with acute HF; (ii) increased mean CWT correlated with poor response to oral loop diuretics as an initial treatment, whereas it did not correlate with response to intravenous loop diuretics; and (iii) discrimination of non-responders to initial oral loop diuretics resulted in a sensitivity of 0.772 and a specificity of 0.733 using a mean CWT cut-off value of ≥3 mm. The novelty of the present study was the indication of the strong correlation between increased intestinal wall thickness and oral loop diuretic resistance. Moreover, intestinal oedema may be one of the key factors that reduce the bioavailability of oral loop diuretics.

**Diuretic resistance**

Loop diuretics are the most widely used diuretics in the treatment of HF. However, physicians often encounter patients who are poorly responsive to loop diuretics, which is referred to as diuretic resistance. Patients with diuretic resistance are known to be at higher risk for adverse events. Diuretic resistance has been attributed to a complex interplay of cardiac...
and renal dysfunction and specific renal adaptation/escape mechanisms, such as neurohormonal activation and braking phenomenon. Results of a prospective cohort designed to specifically to investigate mechanisms of diuretic resistance has been anticipated. Moreover, it is necessary to consider bioavailability in the treatment of HF with oral diuretics. It is known that oral loop diuretics exhibit widely varying bioavailabilities between patients.

The present study revealed one of the patient profiles of reduced bioavailability of oral loop diuretics; that is, intestinal wall thickness and oral loop diuretic resistance had a strong correlation. In contrast, intravenous loop diuretics unaffected by intestinal absorption showed no reduction in diuretic responsiveness associated with increased intestinal wall thickness. In general, management strategies for diuretic resistance include increasing the diuretic dose, changing from oral to intravenous administration route, and/or switching to other drugs. Our results advocate the use of intravenous loop diuretics or other diuretic strategy as an initial HF treatment in patients with a mean CWT ≥ 3 mm.

We also evaluated the incidence of adverse events. The positive correlation found between increased diuretic dosage and adverse events is consistent with previous report. The finding of non-responders to initial diuretic treatment is also consistent with previous reports of significantly worse outcomes.

Heart failure and intestinal oedema

Studies have reported the presence of intestinal oedema in patients with advanced HF. It is believed that intestinal oedema is caused by various factors in the HF settings. First, there are haemodynamic effects caused by systemic congestion and decreased cardiac output in patients with HF. Intestinal oedema was also reported to be associated with right-sided HF and left ventricular diastolic dysfunction. In the present study, PV-CSA and PV-Cl were found to correlate with mean CWT, and PV-CSA, PV-PI, and PV-Cl were found to correlate with loop diuretic dose at enrolment. This finding suggests that portal congestion from systemic congestion due to HF can cause intestinal oedema and diuretic resistance.

Congestion of the intestinal microcirculation caused by HF results in ischemia of the intestinal mucosa, leading to the disruption of the intestinal barrier and bacterial overgrowth. This is believed to be associated with systemic inflammation and cardiac cachexia in patients with HF. Changes in the intestinal wall are also believed to be associated with drug absorption and metabolism. The lack of association between intestinal wall thickness and responsiveness to intravenous loop diuretics in the present study was presumably due to lower intestinal absorption of such agents. In the present study, estimated glomerular filtration rate was identified as an independent factor for the poor responsiveness to intravenous loop diuretics, which is consistent with previous reports. We also found that patients with a mean CWT of ≥3 mm, the cut-off value for non-responder discrimination to initial oral loop diuretics, had significantly worse outcomes. This suggests that a mean CWT cut-off value of ≥3 mm is important for identifying patients with not only poor responsiveness to oral loop diuretic but also worse outcomes.

Limitations

The present study had some considerable limitations. Because we enrolled a small number of patients at a single centre, the possibility of some selection bias could not be excluded. Subgroups stratified by dose of loop diuretics had different characteristics that could influence our results. We used multivariate analysis to minimize the effect of differences in patient characteristics. The evaluation of diuretic response was conducted retrospectively after patient enrolment; thus, the design of the present study might not have an accurate predictive value of intestinal findings on initial diuretic responsiveness. We assumed 40 mg of oral furosemide to be equivalent to 20 mg of intravenous furosemide. This was assumed as a 50% bioavailability of oral loop diuretics. Therefore, caution should be exercised when interpreting our results.

Conclusions

In patients hospitalized with acute HF, there was a strong correlation among the severity of intestinal oedema, required quantities as maintenance loop diuretic doses, and poor responsiveness to oral loop diuretics at admission. In acute HF settings with multiple organ damage, it is important to consider the bioavailability of drugs for drug selection and route of administration.

Conflict of interest

The authors have 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. Representative ultrasonographic images to evaluate PV blood flow and CWT. Increased CSA, PI and CI at PV are...
presented in patients with portal congestion, while increased CWT is presented in patients with intestinal edema. PI and CI were calculated using the following formula: 

$$PI = \frac{V_{max} - \text{minimum velocity}}{\text{mean velocity}}; \quad CI = \text{CSA/mean velocity}.$$ 

A colon wall has five layers. Layer 1 (high echoic) is also known as adventitia (or serosa with subserosal fat), layer 2 (low echoic) as muscularis propria, layer 3 (high echoic) as submucosa, layer 4 (low echoic) as deep mucosa, and layer 5 (high echoic) as interface echo and superficial mucosa. We measured the distance between outermost region of the layer 1 and innermost of the layer 5 for each colonic wall. 

$$PV = \text{portal vein}, \quad CWT = \text{colon wall thickness}, \quad \text{CSA} = \text{cross sectional area}, \quad V_{max} = \text{maximum velocity}, \quad BFV = \text{blood flow volume}, \quad PI = \text{pulsatility index}, \quad CI = \text{congestion index}.$$ 

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