

## Ultrasound Assessment of Kidney Volume in Patients with Acute Decompensated Heart Failure: A Predictor of Diuretic Resistance

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### ABSTRACT

**Background** Diuretics are essential for treating acute decompensated heart failure (ADHF), but the response is inconsistent. This study aimed to clarify whether kidney volume as assessed by ultrasound (US) predicts diuretic resistance in patients with ADHF.

**Methods** We enrolled 29 patients with ADHF and 32 controls. Height-adjusted kidney volume was assessed by US. We divided patients into two groups based on the median value of total daily use of furosemide (intravenous dose plus  $0.5 \times$  oral dose of furosemide equivalents) during 3 days from admission.

**Results** Patients with ADHF had a significantly smaller left kidney volume than did control subjects ( $27.7 \pm 10.0$  vs.  $32.8 \pm 8.8$  mL/m,  $P < 0.05$ ). Patients in the high-dose furosemide group ( $\geq 51.7$  mg/d) had a significantly lower estimated glomerular filtration rate (eGFR) and a significantly smaller kidney volume than did those in the low-dose furosemide group (eGFR:  $43.9 \pm 20.4$  vs.  $60.8 \pm 21.6$  mL/min/1.73 m<sup>2</sup>, left kidney volume:  $23.2 \pm 5.2$  vs.  $32.6 \pm 11.0$  mL/m, right kidney volume:  $26.5 \pm 7.5$  vs.  $32.6 \pm 7.9$  mL/m, all  $P < 0.05$ ). Multivariate logistic analysis showed that left kidney volume, but not eGFR, was independently associated with the requirement of high-dose furosemide (odds ratio: 0.856, 95% confidence interval: 0.735–0.997,  $P < 0.05$ ).

**Conclusion** Kidney volume as assessed by US is a useful predictor of diuretic resistance in patients with ADHF.

**Key words** acute decompensated heart failure; diuretic resistance; kidney volume; ultrasound examination

A lack of adequate relief of symptoms is associated with a longer hospital stay and increased mortality. Therefore, early and effective decongestion for improving outcomes in acute decompensated heart failure (ADHF) is important.<sup>1,2</sup> Intravenous furosemide is currently prescribed for approximately 90% of hospitalized patients with ADHF to relieve congestion.<sup>3</sup> However, there is an ADHF subpopulation with diuretic resistance who are at high risk for morbidity and mortality.<sup>4</sup> Previous studies have shown that renal impairment is one of the determinants of a poor diuretic response in patients with ADHF.<sup>5–8</sup> In a stable hemodynamic state, serum creatinine levels, estimated glomerular filtration rate (eGFR), and blood urea nitrogen (BUN) levels are good parameters for renal function.<sup>9</sup> However, in ADHF, several factors affect the value of these renal biomarkers<sup>7, 10, 11</sup> and a conventional renal function test may be insufficient to identify patients at high risk for diuretic resistance.<sup>12, 13</sup>

Kidney volume is decreased with glomerular sclerosis and tubular atrophy. Kidney volume is a simple estimate of renal reserve and function in patients with suspected renal diseases.<sup>14</sup> However, the relationship between kidney size and diuretic resistance in ADHF remains unknown. The present study aimed to clarify whether kidney volume as assessed by ultrasound (US) predicts diuretic resistance in patients with ADHF.

### SUBJECTS AND METHODS

#### Subjects

The present study enrolled 29 consecutive patients with ADHF who were hospitalized in Tottori University Hospital from April 2014 to November 2015. They agreed to participate in this study within 48 hours after

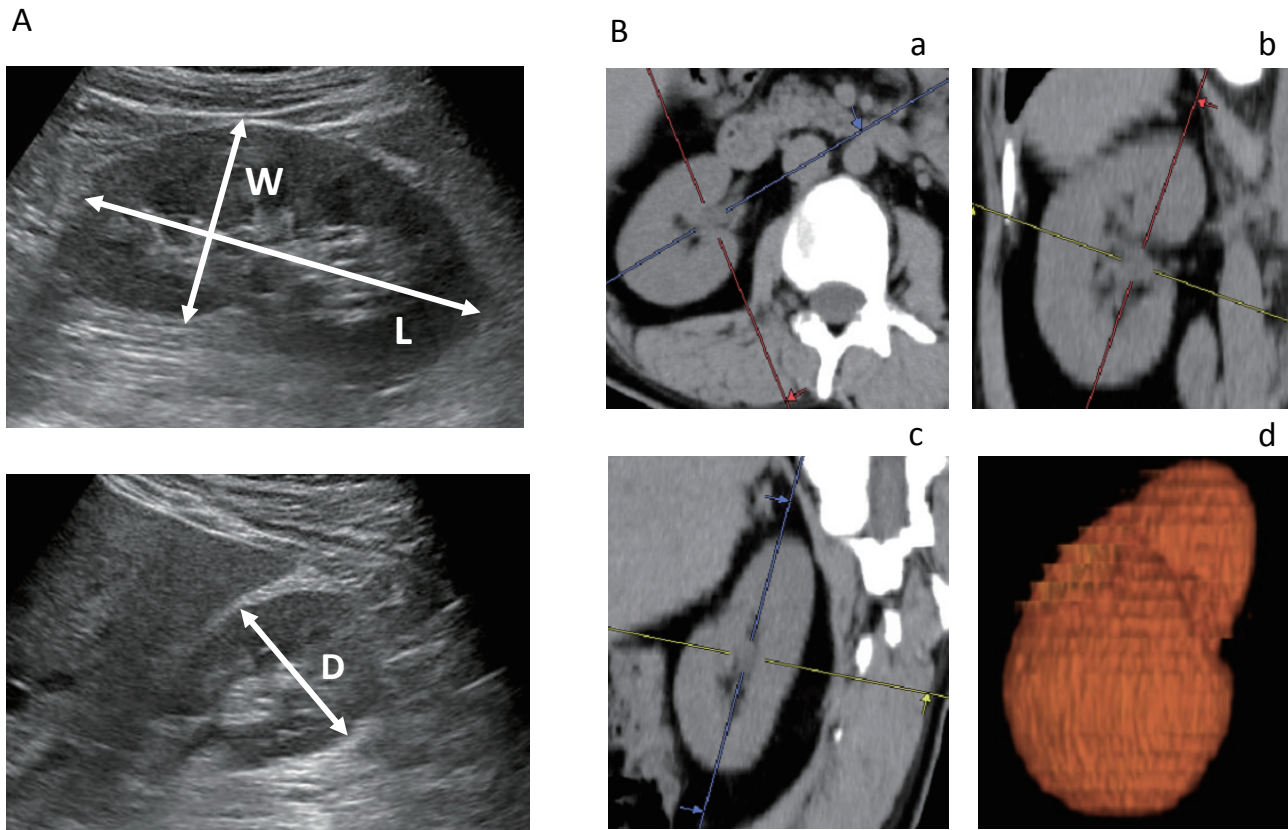
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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CKD, chronic kidney disease; CT, computed tomography; D, depth; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; IABP, intra-aortic balloon pumping; IAP, intra-abdominal pressure; i.v., intravenous; JVD, jugular vein dilation; L, length; LVEF, left ventricular ejection function; MRA, Mineralocorticoid receptor antagonist; NPPV, noninvasive positive pressure ventilation; PCPS, percutaneous cardiopulmonary support; US, ultrasound; W, width



**Fig. 1.** Representative ultrasonic images and computed tomography images for measurement of kidney size. **A:** Representative ultrasonic images. **B:** Representative computed tomography images, **a:** axial image, **b:** coronal image, **c:** sagittal image, and **d:** three-dimensional reconstructive image. D, depth; L, maximum length; W, width.

hospitalization. ADHF was defined as new-onset decompensated heart failure or decompensation of chronic heart failure as previously described.<sup>15</sup> Acute coronary syndrome was excluded. Heart failure (HF) was defined according to Framingham criteria, together with pulmonary congestion on X-rays or pulmonary hypertension as evaluated by Doppler echocardiography. The control group consisted of 32 age- and sex-matched patients without a previous history of HF who were hospitalized for inspection of the gastrointestinal tract or the liver. Patients with malignancy, a unilateral kidney, polycystic kidney disease, and those who received regular hemodialysis were excluded.

### Data collection

Medical records were reviewed for demographics, laboratory data, echocardiograms, medications, and therapeutic response. All measurements were obtained on admission. Kidney volume was assessed by an abdominal US examination within 48 hours after hospitalization. The estimated glomerular filtration rate (eGFR) was determined by the modified Modification of Diet and

Renal Disease study formula for Japanese:  $eGFR = 194 \times (\text{age}^{-0.287}) \times (\text{serum creatinine}^{-1.094}) \times (0.739 \text{ if female})$ .<sup>16</sup> We defined the severity of chronic kidney disease (CKD) based on the guideline of CKD<sup>9</sup> as follows: normal,  $eGFR \geq 90 \text{ mL/min/1.73 m}^2$ ; mild,  $eGFR \geq 60$  and  $< 90 \text{ mL/min/1.73 m}^2$ ; moderate,  $eGFR \geq 30$  and  $< 60 \text{ mL/min/1.73 m}^2$ ; and severe,  $eGFR < 30 \text{ mL/min/1.73 m}^2$ . We evaluated the therapeutic response in the acute phase, including total urine volume, change in body weight, and improvement of New York Heart Association class and signs of congestion, during the first 3 days from admission. All of the patients received intravenous (i.v.) furosemide for 3 days. At our hospital, the initial i.v. dose of furosemide was 40 mg/d according to the European Society of Cardiology (ESC) guidelines.<sup>17</sup> After judgement of response to furosemide every a few hours, the attending physician changed the i.v. dose of furosemide to maintain water balance appropriately.

The same quantity of oral diuretics before hospitalization was continued during this period. The dose of oral loop diuretics was converted to furosemide equivalents as follows: 60 mg of azosemide = 40 mg of furosemide.<sup>18, 19</sup>

Total daily use of furosemide was defined as the i.v. dose of furosemide plus  $0.5 \times$  oral dose of furosemide equivalents for 3 days, taking into account biological availability as previously described.<sup>20</sup> We defined a high dose of furosemide as  $\geq 51.7$  mg/d or based on the median value of total daily use of furosemide. The patients were divided into two groups: low-dose group ( $< 51.7$  mg/d,  $n = 16$ ) and high-dose group ( $\geq 51.7$  mg/d,  $n = 13$ ).

### Renal US examination

All renal US examinations were performed using standard grayscale B-mode imaging on an Aplio 500 Ultrasound System (Toshiba Medical Systems, Tochigi, Japan) with a 3.5-MHz convex transducer. One experienced US physician measured all US parameters. Renal length measurements were performed with patients in the supine position using US. The maximum renal length (L) and width (W) were obtained from longitudinal images in planes ranging from sagittal to coronal. The depth (D) was obtained from transverse images of the mid-kidney acquired in the plane perpendicular to the longitudinal plane (Fig 1A).

Kidney volume was determined using the formula for an ellipsoid ( $\pi/6 \times L \times W \times D$ ),<sup>21</sup> and was adjusted for the individual's height as previously described.<sup>22</sup>

### Kidney volume as assessed by computed tomography

The accuracy of kidney volume as calculated with US was evaluated by comparing it with that assessed by computed tomography (CT). Eleven patients with ADHF underwent thoracic and abdominal CT to identify the cause of infection and pleural effusion on admission to hospital. In this study, we used a 3D-imaging analysis system (SYNAPSE VINCENT; Fuji Photo Film, Tokyo, Japan) to calculate bilateral kidney volume (Fig. 1B). This system is available for automatic extraction of organ and automatic volume measurement, and its application with organs of the whole body has been reported.<sup>23</sup>

This study conformed with the principles outlined in the Declaration of Helsinki and was approved by the institutional review board for human investigation at Tottori University Hospital (approval number: 2467). Written informed consent was provided by each subject.

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation for normally distributed variables, and median and interquartile range for non-normally distributed variables. The normality of distribution was assessed by the Kolmogorov–Smirnov test. Differences in continu-

ous variables between the two groups were compared using the *t*-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables are expressed as percentages. Categorical variables were compared using Fisher's exact test. Correlations of continuous variables between the two groups were tested by Spearman's rank correlation coefficient and Bland–Altman plots. Multivariate logistic regression models were performed to assess the independent predictors of the requirement for high-dose furosemide. All baseline variables with  $P < 0.05$  in univariate analysis were entered into the analysis. A  $P$  value  $< 0.05$  was considered significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0), and XLSTAT for Microsoft Excel (Microsoft, Redmond, WA).

## RESULTS

### Patients' characteristics between the control and ADHF groups

The patients' characteristics in the ADHF group are shown in Tables 1 and 2. The mean age was  $75 \pm 14$  years and 51.7% were men. The etiology of HF was ischemic heart disease in 24.1%, valvular heart disease in 20.7%, and cardiomyopathy in 24.1% of patients. Mean left ventricular ejection fraction was  $44.2 \pm 18.5\%$ , and HF with preserved ejection fraction ( $> 45\%$ ) was prevalent in 44.8% of patients. More than half of the patients had New York Heart Association class IV and "warm and wet" as assessed by noninvasive classification of ADHF.<sup>24</sup>

The patients' characteristics in the control group are shown in Table 1. The ADHF group had significantly higher levels of BUN and creatinine, and a lower eGFR compared with the control group (all  $P < 0.05$ ). There were no significant differences in other well-known factors related to kidney size, including age, sex, height, and body weight, as well as the prevalence of hypertension and diabetes,<sup>25</sup> between the two groups.

### Kidney volume between the control and ADHF groups

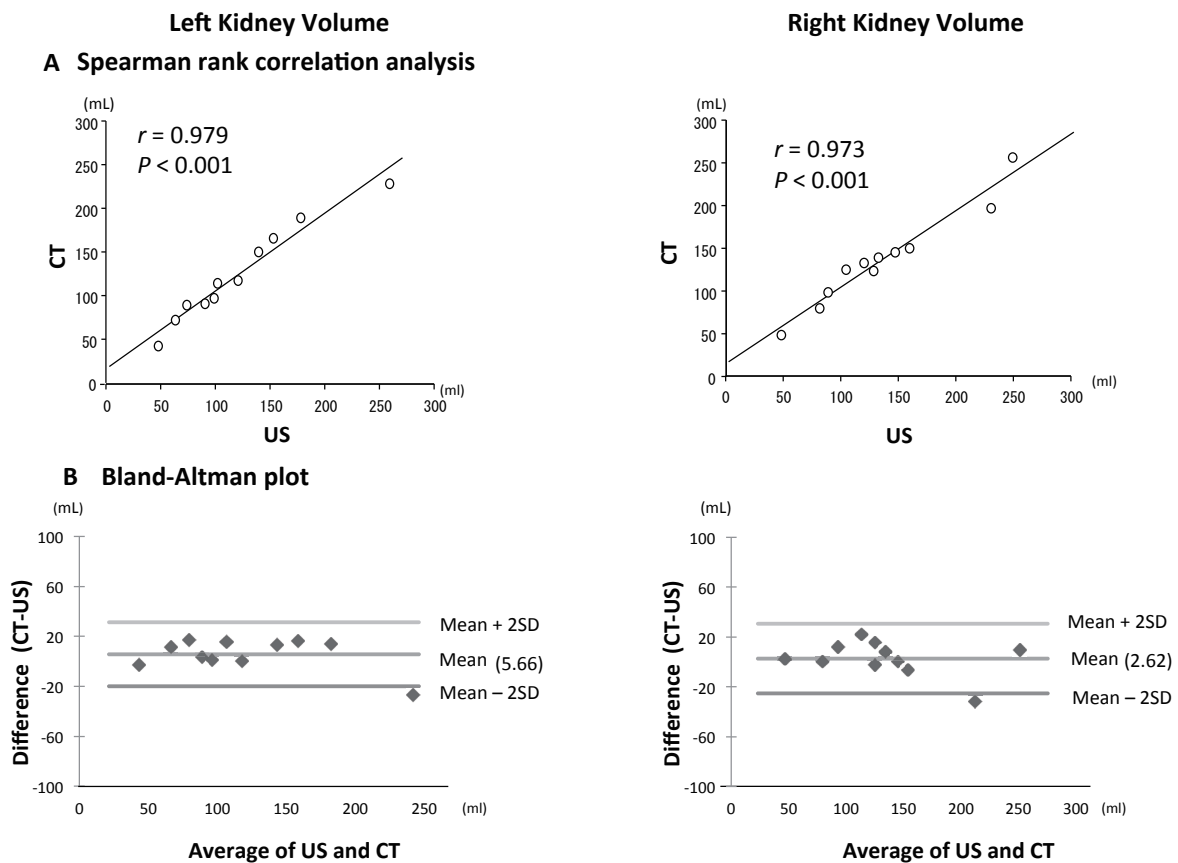
Figure 2 shows the correlation of kidney volume as assessed by US with that as assessed by CT. We found a good linear correlation between the two measurements in Spearman's rank correlation coefficient analysis (left:  $r = 0.979$ ,  $P < 0.001$ ; right:  $r = 0.973$ ,  $P < 0.001$ , Fig. 2A). Bland–Altman plots showed that the mean difference in kidney volume between CT and US was 5.66 mL (left) and 2.62 mL (right), and the standard deviation was

**Table 1. Patients' characteristics in the control and ADHF groups**

	control group (n = 32)	ADHF group (n = 29)	P-value
<b>Demographics</b>			
Age (years)	70 ± 14	75 ± 14	0.158
Male (%)	65.6	51.7	0.278
Height (cm)	160.4 ± 9.4	159.6 ± 8.7	0.729
Body weight (kg)	60.7 ± 11.8	59.3 ± 15.5	0.685
Systolic blood pressure (mmHg)	130 ± 21	124 ± 25	0.509
Heart rate (beats/min)	73 ± 10	85 ± 20	0.057
<b>Comorbidity conditions</b>			
Hypertension (%)	56.5	62.1	0.651
Diabetes (%)	28.1	34.5	0.600
Dyslipidemia (%)	50.0	31.0	0.350
Chronic obstructive disease (%)	22.6	20.7	0.862
<b>Laboratory values</b>			
BUN (mmol/L)	5.2 ± 1.8	9.2 ± 6.2	0.003
Creatinine (umol/L)	72.4 ± 22.0	99.9 ± 57.5	0.015
eGFR (mL /min/1.73 m <sup>2</sup> )	71.0 ± 24.1	53.2 ± 22.4	0.004
Severity of CKD:			0.005
Normal/mild/moderate/severe (%)	18.8/43.8/37.4/0.0	6.9/27.6/55.2/10.3	

Data are mean ± SD or percentage. Severity of CKD was classified as follows: normal, eGFR ≥ 90 mL/min/1.73 m<sup>2</sup>; mild, eGFR ≥ 60 and < 90 mL/min/1.73 m<sup>2</sup>; moderate, eGFR ≥ 30 and < 60 mL/min/1.73 m<sup>2</sup>; and severe, eGFR < 30 mL/min/1.73 m<sup>2</sup>.

ADHF, acute decompensated heart failure; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular rate.



**Fig. 2.** Correlation of kidney volume calculated by US and CT. **A:** Spearman's rank correlation coefficient analysis of the left and right kidneys. **B:** Bland-Altman plots of the left and right kidneys. The mean differences in the volume of CT and US were 5.66 mL (left) and 2.62 mL (right), and the SD was 13.45 mL (left) and 14.28 mL (right). CT, computed tomography; US, ultrasound.

**Table 2. Baseline characteristics of patients with ADHF in the low-dose and high-dose furosemide groups**

	Low dose group (n = 16)	High dose group (n = 13)	P-value
<b>Demographics</b>			
Age (years)	74 ± 13	76 ± 16	0.771
Male (%)	62.5	38.5	0.211
Prior heart failure hospitalization (%)	43.7	46.2	0.902
Height (cm)	161.4 ± 7.9	157.5 ± 9.5	0.240
Body weight (kg)	61.4 ± 18.4	56.7 ± 11.1	0.413
Systolic blood pressure (mmHg)	120 ± 23	129 ± 28	0.322
Heart rate (beats/min)	85 ± 16	87 ± 25	0.785
NYHA class III/IV (%)	75.0/25.0	61.5/38.5	0.454
Noninvasive classification of ADHF:			
Warm/cold, wet/dry	75.0/25.0, 100.0/0.0	84.6/15.4, 84.6/15.4	0.542/0.111
Clinical scenario: 1/2/3/5	25.0/43.8/12.5/18.7	23.1/69.2/7.7/0.0	0.686
LVEF (%)	46.0 ± 20.6	44.1 ± 16.0	0.782
<b>Comorbidities</b>			
Coronary artery disease (%)	18.8	30.8	0.470
Hypertension (%)	62.5	61.5	0.959
Diabetes (%)	23.1	33.3	0.587
<b>Laboratory values</b>			
Sodium (mmol/L)	138.8 ± 4.6	142.0 ± 5.9	0.113
Albumin (g/L)	32.7 ± 7.5	35.2 ± 6.7	0.390
BNP (pg/mL)	1256 (480–1437)	1015 (318–1218)	0.548
BUN (mmol/L)	7.5 ± 2.6	11.3 ± 8.7	0.100
Creatinine (umol/L)	82.2 ± 26.5	121.1 ± 76.6	0.068
eGFR (mL/min/1.73 m <sup>2</sup> )	60.8 ± 21.6	43.9 ± 20.4	0.040
Severity of CKD:			
Normal/mild/moderate/severe (%)	12.5/31.3/56.2/0.0	0.0/15.4/61.5/23.1	0.018
<b>Pre-hospital medication</b>			
ACEI/ARB (%)	50.0	58.3	0.685
β-blocker (%)	38.5	50.0	0.580
MRA (%)	12.5	15.4	0.830
Loop diuretics (%)	31.3	76.9	0.013
Thiazide (%)	12.5	7.7	0.686
Tolvaptan (%)	0.0	0.0	1.000

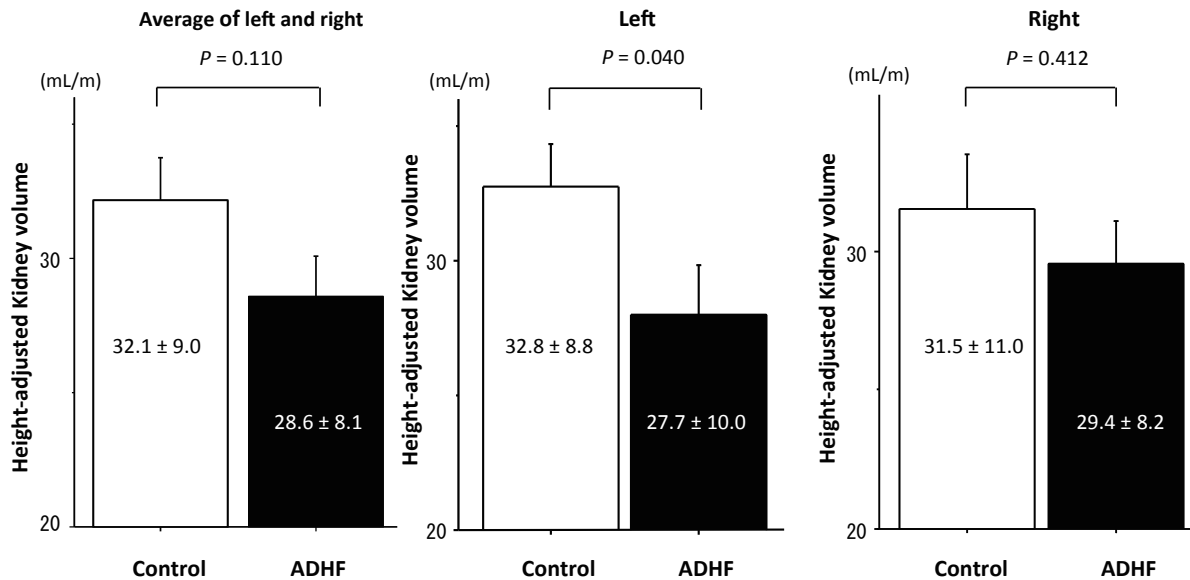
Data are mean ± SD or median (interquartile range). Severity of CKD was classified as follows: normal, eGFR ≥ 90 mL/min/1.73 m<sup>2</sup>; mild, eGFR ≥ 60 and < 90 mL/min/1.73 m<sup>2</sup>; moderate, eGFR ≥ 30 and < 60 mL/min/1.73 m<sup>2</sup>; and severe, eGFR < 30 mL/min/1.73 m<sup>2</sup>. ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

13.45 mL (left) and 14.28 mL (right, Fig. 2B).

Figure 3 shows the height-adjusted kidney volume of the control and ADHF groups. Left kidney volume in the ADHF group was significantly lower than that in the control group (27.7 ± 10.0 mL/m vs. 32.8 ± 8.8 mL/m, *P* < 0.05). Right kidney volume and the mean left and right kidney volumes in the ADHF group were also slightly smaller than those in the control group, but they did not reach significance (29.4 ± 8.2 mL/m vs. 31.5 ± 11.0 mL/m, *P* = 0.412, 28.6 ± 8.1 mL/m vs. 32.1 ± 9.0 mL/m, *P* = 0.110, respectively).

**Characteristics of patients with ADHF in the low-dose and high-dose furosemide groups**

Table 2 shows baseline characteristics of patients with ADHF between the low-dose and high-dose groups. Patients in the high-dose group had a significantly lower level of eGFR than did those in the low-dose group (*P* < 0.05). Serum levels of BUN and creatinine also tended to be higher in the high-dose group than in the low-dose group. The prescription rate of oral loop diuretics before hospital admission was significantly higher in the high-dose group than in the low-dose group (*P* < 0.05). There were no significant differences in age, sex, height, body



**Fig. 3.** Height-adjusted kidney volume in the control and ADHF groups. Patients in the ADHF group had a significantly smaller left kidney volume than those in the control group. ADHF, acute decompensated heart failure.

weight, medical history, and other laboratory data between the two groups.

#### In-hospital treatment and therapeutic response in ADHF in the low-dose and high-dose furosemide groups

Table 3 shows the in-hospital treatment and therapeutic responses during 3 days after admission to hospital. All of the patients received i.v. furosemide for 3 days, and the daily mean i.v. dose was  $37.4 \pm 18.4$  mg/d (20–100.0 mg/d). The dose of oral diuretics prescribed before hospitalization was not changed during this period, and the daily oral dose was  $43.3 \pm 23.8$  mg/d (20.0–120.0 mg/d). Patients in the high-dose group more frequently received a higher daily dose of i.v. furosemide ( $47.4 \pm 18.1$  vs.  $26.3 \pm 11.9$  mg/d,  $P < 0.05$ ), as well as a higher daily dose of oral furosemide ( $56.9 \pm 24.3$  vs.  $32.2 \pm 17.2$  mg/d,  $P < 0.05$ ), compared with those in the low-dose group. Additionally, patients in the high-dose group had a higher prescription rate and dosage of carperitide than did those in the low-dose group (92.3% vs. 56.3%,  $0.021 \pm 0.01$  vs.  $0.010 \pm 0.001$   $\gamma$ , all  $P < 0.05$ ). There were no significant differences in therapeutic responses, including a change in body weight, total urine volume, and improvement of symptoms and congestion between the two groups. Therefore, patients in the high-dose group required more intensive decongestion therapy for the same degree of improvement compared with the low-dose group.

#### Kidney volume in ADHF in the low-dose and high-dose furosemide groups

Figure 4 shows kidney volume in ADHF between the low-dose and high-dose groups. Left and right kidney volumes in the high-dose group were significantly smaller than those in the low-dose group (left:  $23.2 \pm 5.2$  vs.  $32.6 \pm 11.0$  mL/m, right:  $26.5 \pm 7.5$  vs.  $32.6 \pm 7.9$  mL/m, mean of both sides:  $24.9 \pm 3.9$  vs.  $32.6 \pm 8.9$  mL/m, all  $P < 0.05$ ).

Table 4 shows multivariate logistic regression analysis for predicting the requirement of high-dose furosemide. In univariate analysis, eGFR and each kidney volume were significantly associated with high-dose furosemide. In multivariate analysis, left kidney volume, but not eGFR, remained an independent predictor of the requirement of high-dose furosemide (odds ratio: 0.856, 95% confidence interval: 0.735–0.997,  $P < 0.05$ ) (Table 4).

## DISCUSSION

This study showed that kidney volume as assessed by US independently predicted the required dose of furosemide at the acute phase of treatment of ADHF.

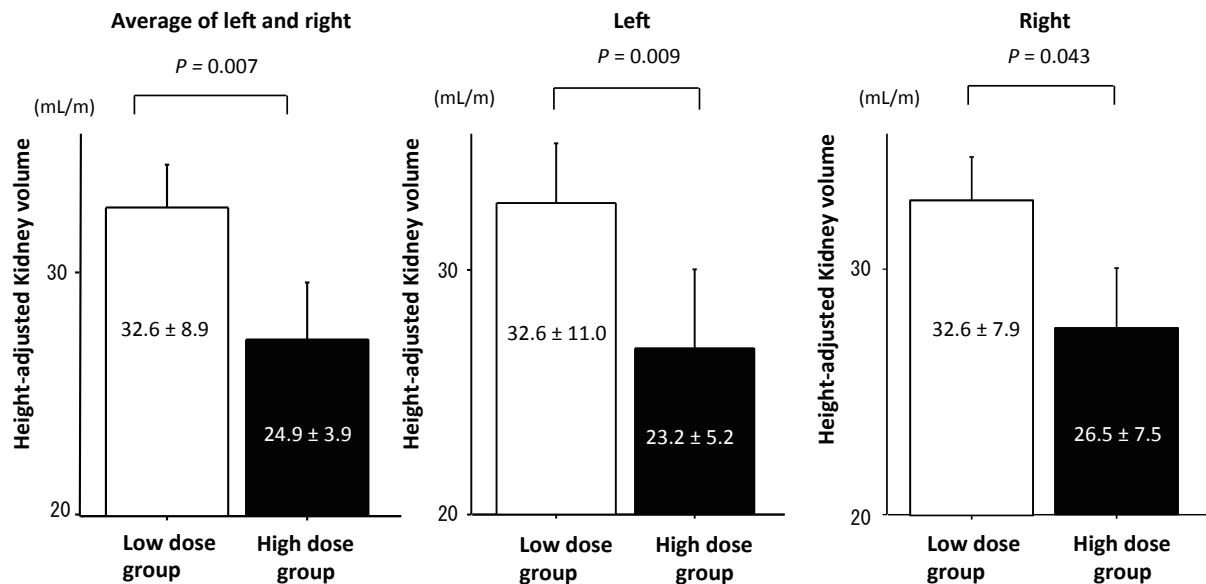
Renal function is one of the determinants of a diuretic response in ADHF.<sup>4–8</sup> However, in ADHF, several factors affect the value of renal function tests. Creatinine levels and eGFR are affected by fluid retention or a decrease in blood pressure.<sup>10</sup> The level of BUN, a marker of reduced glomerular filtration,<sup>26</sup> is also affected by comorbidities, such as liver disease and malnutrition.<sup>27</sup> The

**Table 3. In-hospital management, and therapeutic response of ADHF in the low-dose and high-dose furosemide groups**

	Low dose group (n = 16)	High dose group (n = 13)	P-value
<b>Furosemide</b>			
Daily i.v. dose (mg/day)	26.3 ± 11.9	47.4 ± 18.1	0.001
Daily oral dose (mg/day)	32.2 ± 17.2	56.9 ± 24.3	0.003
Daily total dose (i.v. dose conversion) (mg/day)	42.5 ± 8.6	75.9 ± 18.7	< 0.001
<b>Intravenous drugs</b>			
Carperitide (%)	56.3	92.3	0.031
Mean dose of carperitide (γ)	0.010 ± 0.001	0.021 ± 0.010	0.030
Nitroglycerin (%)	12.5	15.4	0.830
Inotropes (%)	12.5	23.1	0.471
<b>Non-pharmacological management</b>			
NPPV (%)	25.0	38.5	0.454
Intubation (%)	0.0	0.0	1.000
IABP/PCPS (%)	0.0	0.0	1.000
Ultrafiltration (%)	0.0	0.0	1.000
<b>Therapeutic response</b>			
Daily change in body weight, (kg/day)	-0.7 ± 0.5	-0.8 ± 0.5	0.727
Daily urine volume, (mL/day)	2066 ± 683	2012 ± 724	0.841
Improvement of:			
NYHA class (%)	87.5	69.2	0.242
Peripheral edema (%)	50.0	30.8	0.374
Rales (%)	43.8	46.2	0.902
JVD (%)	18.8	15.4	0.820

Data are mean ± SD or percentage.

ADHF, acute decompensated heart failure; IABP, intra-aortic balloon pumping; i.v., intravenous; JVD, jugular vein dilatation; NPPV, noninvasive positive pressure ventilation; NYHA, New York Heart Association; PCPS, percutaneous cardiopulmonary support.



**Fig. 4.** Height-adjusted kidney volume of ADHF in the low-dose and high-dose furosemide groups. Patients in the high-dose group had a significantly smaller kidney volume (left, right) than those in the low-dose group. ADHF, acute decompensated heart failure.

**Table 4. Multivariable logistic regression analyses for predicting the requirement of high-dose furosemide**

	OR	95% CI	P-value
Average of left and right kidney volume	0.831	0.688–1.004	0.055
eGFR	0.973	0.927–1.021	0.263
Left kidney volume	0.856	0.735–0.997	0.045
eGFR	0.969	0.925–1.016	0.195
Right kidney volume	0.921	0.821–1.034	0.163
eGFR	0.966	0.921–1.012	0.149

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

present study showed that, among renal biomarkers, only eGFR was significantly associated with a requirement for a high dose of furosemide. However, by multivariate analysis, eGFR no longer independently predicted diuretic resistance. This finding suggested insufficiency of these conventional markers in identifying patients at a high risk for diuretic resistance.

Kidney volume is a simple estimate of renal reserve and function.<sup>13</sup> Some studies have shown that kidney volume provides useful information on the risk and complications in CKD beyond eGFR and albuminuria.<sup>13,28</sup> A previous study on ADHF reported that a shorter longitudinal kidney length as assessed by CT was associated with a poor diuretic response.<sup>29</sup> In this study, we showed the reliability of US in the measurement of kidney volume compared with CT. US has the advantage of no radiation exposure and can be conducted at the bedside. Therefore, the current study expanded previous findings by demonstrating that kidney volume as assessed by US is a convenient and noninvasive alternative to that as assessed by CT for identifying patients at high risk for diuretic resistance.

Interestingly we found that, in patients with ADHF, left kidney atrophy was predominantly observed, and was independently associated with diuretic resistance. Although this study had a small sample size, and cannot provide conclusive evidence, we speculate several possible mechanisms regarding the relation between the laterality of kidney size and the diuretic response. Davran et al. previously reported that there was a higher prevalence of left kidney atrophy than right kidney atrophy. Of 2417 patients, 1.3% of patients had renal atrophy in the left side compared with 0.2% of patients with renal atrophy in the right side.<sup>30</sup> The cause of left kidney atrophy is unclear, but a potential explanation is anatomical differences in the kidney. The left renal artery is shorter than the right renal artery because of the location of the aorta.<sup>31</sup> Davran et al. speculated that the left kidney is likely to receive a relatively high arterial pressure because of the shorter distance to the heart.<sup>30</sup> This results in endothelial

dysfunction and atherosclerosis, which cause poor perfusion of the left kidney.<sup>31,32</sup> Additionally, the left kidney is in contact with many organs, including the aorta, pancreas, spleen, stomach, small intestine, and colon. However, the right kidney contacts only three organs of the liver, right colon flexure, and duodenum.<sup>31</sup> In ADHF, venous congestion elevates intra-abdominal pressure (IAP).<sup>33</sup> The left kidney is more likely to be compressed by elevated IAP than the right kidney because many organs around the left kidney may form a close space and increase local IAP. Additionally, the left renal vein is approximately two or three times longer than the right renal vein, and is in contact with the aorta.<sup>31</sup> Elevated IAP may also lead to left renal vein compression and congestion,<sup>34</sup> contributing to poor left kidney perfusion and worsened renal function. The dominance of left kidney atrophy remains a matter of speculation. Further investigations are necessary to evaluate the relationship between the laterality of kidney size and renal function.

This study has several limitations. First, there is a large difference in the dose of furosemide used between our study and previous studies conducted in Western countries. A dose trial showed that the daily dose of i.v. furosemide at the acute phase of treatment was approximately 120 mg/d in the low-dose group and 260 mg/d in the high-dose group.<sup>35</sup> However, patients with HF in Japan require a lower dose of furosemide than those in Western countries. A phase III, randomized, double-blind, placebo-controlled study (QUEST study) assessed the efficiency and safety of tolvaptan in Japanese patients with ADHF.<sup>36</sup> This previous study showed that volume overload, despite the use of an average daily dose of furosemide  $\geq 40$  mg, is defined as diuretic resistance. In our study, patients in the high-dose group received a high dose of furosemide of  $\geq 40$  mg/d (daily oral dose of  $56.9 \pm 24.3$  mg/d plus a daily i.v. dose of  $47.4 \pm 18.1$  mg/d), which indicated that they were accompanied by diuretic resistance. Second, this study had a small sample size and low statistical power. Furthermore, the effect of kidney volume on clinical outcomes was unclear. Fur-



ther well-designed, large, prospective trials are required to clarify these issues. In conclusions, Kidney volume as assessed by US is helpful in identifying patients with ADHF at a high risk for diuretic resistance.

*The authors declare no conflict of interest.*

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