Body fluid control by diuresis is the foundation for the treatment of acute heart failure (AHF). Although excessive diuresis is essential for relieving symptoms associated with AHF, it can lead to the worsening of renal function (WRF), which is a common complication encountered during hospitalization for AHF that is associated with significant morbidity and mortality.1–4 Previous reports have identified the history of hypertension, diabetes mellitus, chronic kidney disease, and the use of diuretics as predictors of WRF in patients requiring AHF hospitalization.1

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In particular, the use of diuretics leading to WRF has received considerable clinical attention.1,5 The main underlying mechanism is thought to be related to plasma volume reduction (PVR) with the subsequent reduction of renal perfusion and activation of the renin–angiotensin–aldosterone system.6 Previous studies have shown that PVR, represented by hemoconcentration, is associated with WRF.7,8 Therefore, the maintenance of optimal PVR without the resultant impairment of renal function is essential for AHF management.

Because AHF is a heterogeneous condition, the impact of PVR may differ depending on AHF subclasses based on ejection fraction. Abramov et al9 reported that patients with heart failure with preserved ejection fraction (HFpEF) had a lower total blood volume (ie, the intravascular volume) than those with heart failure with reduced ejection fraction (HFrEF). Similarly, Schwartzenberg et al10 reported a greater stroke volume reduction in HFpEF than in HFrEF after vasodilation treatment, indicating the presence of occult intravascular hypovolemia in HFrEF. Therefore, we aimed to compare the effect of estimated PVR on renal function during AHF hospitalization between patients with HFpEF and HFrEF from the West Tokyo Heart Failure Registry.

Background—The prognostic relevance of plasma volume reduction (PVR) in acute heart failure patients remains unclear because of the confounding hemodynamic effect of left ventricular ejection fraction impairment on kidney function.

Methods and Results—Subjects enrolled in the West Tokyo Heart Failure Registry were examined. The PVR at admission and discharge was estimated from the subjects’ body weight and its deviation from the ideal body weight. Patients in the top tertile of estimated PVR were classified as PVR+. Of the 381 patients with acute heart failure, 181 (47.5%) had heart failure with preserved ejection fraction (HFpEF). Estimated PVR was associated with worsening renal function in the HFpEF (odds ratio, 3.28; 95% confidence interval, 1.55–6.96; P=0.002) but not in the heart failure with reduced ejection fraction cohort (odds ratio, 1.22; 95% confidence interval, 0.61–2.42; P=0.57). This association in the HFpEF cohort remained significant after adjusting for a history of hypertension and diabetes mellitus and the estimated glomerular filtration rate (odds ratio, 3.34; 95% confidence interval, 1.52–7.33; P=0.003). The use of intravenous diuretics was a significant predictor of PVR in the HFpEF and heart failure with reduced ejection fraction groups.

Conclusions—The effect of estimated PVR differs by HF type, and the estimated PVR during hospitalization is a predictor of worsening renal function in patients with HFpEF but not in heart failure with reduced ejection fraction.

Clinical Trial Registration—URL: http://www.umin.ac.jp/ctr/index-j.html. Unique identifier: UMIN000001549.

Key Words: diuretics ■ heart failure ■ heart failure, diastolic ■ plasma

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Methods

Study Design

Data from the West Tokyo Heart Failure Registry, which was obtained between January 2007 and August 2014, were retrospectively analyzed. The West Tokyo Heart Failure Registry is a multicenter, observational, prospective cohort registry that includes all patients requiring hospitalization with a diagnosis of AHF for the first time according to the Framingham AHF criteria. The present study was conducted at 2 university hospitals and 2 tertiary referral hospitals, all of which are in Tokyo, Japan. Most registered patients were Japanese. The present study was approved by each center’s ethics review committee, and all the patients provided informed consent.

Eligibility Criteria

From the 947 patients enrolled in the West Tokyo Heart Failure Registry, those with a recorded serum hemoglobin, serum creatinine, body weight at admission and discharge, and left ventricular ejection fraction data during hospitalization were included in this study (480 patients). The estimated glomerular filtration rate, which was adjusted for age and sex, was calculated from the serum creatinine in each patient. To minimize errors associated with the estimation of PV, patients with serum hemoglobin levels ≤7 g/dL at admission (6 patients whose erythrocyte volumes were likely to change during hospitalization), estimated glomerular filtration rate <15 mL/min at admission (22 patients in whom the primary cause of WRF may not have been PVR), and the duration of hospitalization >30 days (63 cases whose blood composition was likely to change profoundly during hospitalization) were excluded; in addition, 8 patients who died during hospitalization were also excluded.

PV Estimation

The total blood volume was estimated using a deviation from the patients’ body weight from their ideal weight as previously reported (ideal body weight method). Briefly, from the deviation of real body weight from the ideal one, which was normalized for height, the ratio of the total blood volume to body weight was determined for each patient. Then the estimated PV was calculated using the following equation:

\[
\text{Estimated PV} = \text{body weight} \times (\text{designated total blood volume} / \text{body weight ratio}) \times (1-\text{hematocrit})
\]  

The estimated PVR rate, defined as the ratio of predischARGE estimated PV to the estimated PV on admission, was then calculated in each patient.

This method was validated by a study that analyzed relatively large healthy volunteers (160) who underwent scintigraphy with radiolabeled albumin. In addition, we multiplied 1.31 to the estimated PV to the estimated PV on admission, was then calculated in

\[
\text{Estimated PV (ideal body weight method)} = \text{body weight} \times (\text{designated total blood volume} / \text{body weight ratio}) \times (1-\text{hematocrit}) \times 1.31
\]

Patients in the top tertile of the estimated PVR rate were classified as the PVR+ group. Patients with HFP EF were defined as patients with AHF with left ventricular ejection fraction of ≥40% at admission. WRF was defined as a ≥20% decrease in the estimated glomerular filtration rate during hospitalization.

In addition, patients in the top tertile of the hematocrit increase during hospitalization were defined as the hemococoncentration group. The association between hemococoncentration and WRF was also analyzed.

The association between the estimated PVR and long-term prognosis was examined. Cardiac mortality, defined as the composite of sudden death, death because of heart failure, and myocardial infarction, was used as the primary end point for long-term prognosis. In addition, the association between WRF and cardiac mortality in the HFP EF and HFR EF cohorts was also individually analyzed. Dedicated coordinators and investigators obtained follow-up data from the patients’ hospital records and telephonic interviews with patients or their family members. These data were renewed once every year for all patients.

Statistical Analysis

Values with a normal distribution were reported as mean±SDs. Ordinal variables were summarized using a median with 25 and 75 percentiles. The clinical characteristics of patients with and without estimated PVR in the HFP EF and HFR EF groups were compared using Student t test, Pearson χ2 test, and Mann–Whitney U test as appropriate. Univariate logistic regression analysis was performed to examine the association between the estimated PVR and WRF in the HFP EF and HFR EF groups. Multivariable logistic regression analysis was used to adjust for known predictors of WRF among the patients with AHF. The log-rank test was used to assess the effects of estimated PVR on the long-term outcomes. All statistical analyses were performed using SPSS, version 21 (IBM, Corp, Armonk, NY). A P value of <0.05 was considered statistically significant.

Results

Study Population

A total of 381 patients (65.9% men) were included in the present study, of which 181 patients (47.5%) comprised the HFP EF group (Figure). Table 1 shows the patients’ background characteristics according to the presence and absence of estimated PVR for each group (HFP EF and HFR EF). Patients with preserved EF tended to be older (72.2 versus 66.6 years; P<0.001) and were more frequently women (39.2% versus 30.0%; P=0.08). Other characteristics such as age, sex, renal function, length of hospitalization, electrolyte value, New York Heart Association classification, and plasma brain natriuretic peptide concentration did not significantly differ between the PVR+ and PVR− patients regardless of EF.

Predictors of Estimated PVR

Intravenous diuretics were more frequently used in the PVR+ group of the HFR EF and HFP EF cohorts (Table 1). The PVR+ group also showed external edema on admission more frequently. In addition, hemoglobin was significantly lower in the PVR+ patients than in the PVR− patients from the HFP EF group but not in the HFR EF group. The absolute estimated PVR was not statistically different between HFP EF and HFR EF, both in the PVR+ and PVR− patients.
Predictors of Worsening Renal Function

WRF occurred in 36 (19.9%) patients of the HFpEF group and in 46 (23.0%) patients of the HFrEF group during hospitalization. However, an association between PVR+ and WRF was observed solely in the HFpEF group (odds ratio [OR], 3.28; 95% confidence interval [CI], 1.55–6.96 and OR, 1.22; 95% CI, 0.61–2.42 for the HFpEF and HFrEF groups, respectively). This association remained significant after adjusting for the known predictors of WRF such as a history of hypertension, diabetes mellitus, and estimated glomerular filtration rate on admission (OR, 3.34; 95% CI, 1.52–7.33; P=0.003; Table 2). We also analyzed the association between hemoconcentration and WRF. The association between hemoconcentration and WRF was again solely in the HFpEF group.

Table 1. Patients’ Background Characteristics According to the Presence/Absence of PVR in the HFpEF and HFrEF cohorts

<table>
<thead>
<tr>
<th></th>
<th>HFpEF</th>
<th>HFrEF</th>
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<tbody>
<tr>
<td></td>
<td>PVR (n=60)</td>
<td>Non-PVR (n=121)</td>
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<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>74.0±12.0</td>
<td>71.3±13.7</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>53.3</td>
<td>65.3</td>
</tr>
<tr>
<td>NYHA (median, 25 and 75 percentiles)</td>
<td>3, 2, 4</td>
<td>3, 2, 3</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>14.7±6.4</td>
<td>15.3±6.3</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN, %</td>
<td>61.0</td>
<td>59.3</td>
</tr>
<tr>
<td>DM, %</td>
<td>35.0</td>
<td>30.5</td>
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<tr>
<td>Ischemic pathogenesis, %</td>
<td>15.0</td>
<td>24.0</td>
</tr>
<tr>
<td>CKD, %</td>
<td>38.3</td>
<td>34.7</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>55.6±8.4</td>
<td>55.1±8.5</td>
</tr>
<tr>
<td>LVDd, mm</td>
<td>47.8±8.1</td>
<td>48.2±6.9</td>
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<tr>
<td>LVDs, mm</td>
<td>32.4±6.8</td>
<td>32.9±7.0</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>44.3±9.3</td>
<td>45.6±11.8</td>
</tr>
<tr>
<td>IVCd, mm</td>
<td>13.9±0.39</td>
<td>16.0±0.47</td>
</tr>
<tr>
<td>Laboratory data on admission</td>
<td></td>
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<tr>
<td>Serum Cr, mg/dL</td>
<td>1.05±0.54</td>
<td>1.15±0.62</td>
</tr>
<tr>
<td>Hb, mg/dL</td>
<td>11.6±2.1</td>
<td>12.7±2.4</td>
</tr>
<tr>
<td>Serum Na, mEq/L</td>
<td>139.5±5.16</td>
<td>139.6±3.66</td>
</tr>
<tr>
<td>Serum BNP, pg/mL</td>
<td>565.2±568.7</td>
<td>594.4±604.8</td>
</tr>
<tr>
<td>Physical examination on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVD, %</td>
<td>62.1</td>
<td>48.2</td>
</tr>
<tr>
<td>External edema, %</td>
<td>85.0</td>
<td>57.8</td>
</tr>
<tr>
<td>SIII, %</td>
<td>58.3</td>
<td>51.7</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
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<tr>
<td>Intravenous diuretics, %</td>
<td>70.0</td>
<td>52.9</td>
</tr>
<tr>
<td>ACEI, %</td>
<td>16.7</td>
<td>8.3</td>
</tr>
<tr>
<td>ARB, %</td>
<td>30.0</td>
<td>43.0</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>35.6</td>
<td>38.3</td>
</tr>
<tr>
<td>Plasma volume estimation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR rate (percentage of plasma volume on admission)</td>
<td>15.9±4.8</td>
<td>1.3±7.3</td>
</tr>
<tr>
<td>Absolute PVR, mL</td>
<td>486.5±187.8</td>
<td>50.8±184.0</td>
</tr>
<tr>
<td>Absolute PVR per hospital day, mL/d</td>
<td>40.1±27.2</td>
<td>2.2±31.5</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD for variables with normal distributions and as a median (interquartile range) for variables with non-normal distribution. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CKD, chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL/min; Cr, creatinine; DM, diabetes mellitus; Hb, hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; IVCd, inferior vena cava diameter; JVD, jugular vessel dilatation; LAD, left atrial diameter; LVDd, diastolic left ventricular diameter; LVDs, systolic left ventricular diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVR, plasma volume reduction; and SIII, third heart sound.
HFpEF (OR, 2.83; 95% CI, 1.34–5.99 and OR, 1.38; 95% CI, 0.70–2.73 for the HFpEF and HFrEF groups, respectively).

**Long-Term Prognosis and Estimated PVR**
During the median follow-up period of 524 days, 24 cardiac mortality events were observed. The numbers of cardiac mortality events in the PVR+ and PVR− patients were 3 (4.9%) and 7 (5.8%), respectively, in the HFrEF group, and were 2 (3.0%) and 12 (9.0%), respectively, in the HFpEF group. According to the log-rank analysis, the incidence of cardiac mortality did not differ significantly between the PVR+ and PVR− patients in either patient group. In addition, we compared the cardiac mortality rate between WRF and non-WRF patients in the HFpEF and HFrEF cohorts. The cardiac mortality rates in patients with WRF and non-WRF were 2.8% and 6.2%, respectively, in the HFpEF group (log-rank test, P=0.33) and were 6.5% and 7.1%, respectively, in the HFrEF group (P=0.84). The mortality rate did not seem to differ between patients with and without WRF in either of the patient groups.

**Discussion**
In the present study, the estimated PVR was associated with WRF in the HFpEF group but not in the HFrEF group. This difference probably reflects the pathophysiological difference between HFpEF and HFrEF. In HFpEF, volume distribution is the predominant cause of congestion rather than volume overload, which is typically the main cause of congestion in HFrEF. In this study, diuretics were more frequently used in PVR+ patients than in PVR− patients. Furthermore, external edema, a sign of a fluid shift from the plasma to the extravascular space, was also more frequently observed in the PVR+ group. Therefore, the findings imply that PVR caused by diuresis and impaired fluid refilling from the extravascular space to the plasma can trigger WRF more easily in HFpEF than in HFrEF.

Optimizing decongestion therapies without compromising renal function is important during the treatment of patients with AHF. To achieve this goal, decongestion must maintain pace with plasma refilling from the extravascular space to the intravascular space. Previous studies have assessed intravascular volume loss on the basis of hemoconcentration. Hence, we also analyzed the association between hemoconcentration and WRF. In accordance with the findings obtained on estimated PVR, WRF was more frequently observed in patients with hemoconcentration in HFpEF, and this association was not observed in HFrEF. The consistent association between the PVR and WRF in HFpEF, which was obtained from the estimated PVR and hemoconcentration, may imply the universality of our notion. Furthermore, previous studies have focused on the association between elevated central venous pressure and WRF. Theoretically, PVR leads to a reduction in central venous pressure, but as shown previously, net-fluid loss does not predict this reduction and simply lowering the central venous pressure does not result in improved renal function.

We examined several patient characteristics associated with estimated PVR. The use of intravascular diuretics was associated with estimated PVR. This finding supports the theoretical link between diuresis and estimated PVR; therefore, the PVR must be carefully monitored when treating patients with HFpEF with diuretics. External edema on admission was more frequently observed in PVR+ patients than in PVR− patients in the HFpEF and HFrEF cohorts, which suggests that the impaired fluid refilling from the extravascular space to the intravascular space may cause PVR.

Previous studies have reported that patients with lower hemoglobin, serum albumin, and serum total protein tend to develop hemoconcentration during AHF hospitalization. In the present study, patients with a lower hemoglobin tended to be PVR+ during hospitalization solely in the HFpEF cohort. Although the exact underlying mechanism is unclear, it is possible that because of their lower plasma osmotic pressure, patients with diluted blood are susceptible to the sequelae of decongestion therapy.

**Clinical Implications**
The findings of this study suggest that avoiding excessive PVR helps reduce the risk of WRF, especially in patients with HFpEF in whom congestion is mainly caused by the fluid shift from the intravascular space to the extravascular space. Considering that the prognosis of HFpEF has not improved substantially during the past 2 decades, it is necessary to re-evaluate existing therapy. The information available on diuretic therapy optimization is limited, and no data available thus far indicate how to prevent WRF from developing in...
patients with HFpEF.\textsuperscript{23} Thus, avoiding PVR and subsequent WRF in HFpEF is the only rational treatment choice, and the estimation of PV using the ideal body weight system is a practical way to achieve this goal.

In the present study, we also analyzed the association between estimated PVR and long-term prognosis. Testani et al\textsuperscript{10} previously showed an association between hemoconcentration and decreased mortality in HFrEF, and they attributed this finding to efficient decongestion. Although the same trend was observed in the HFrEF cohort in this study, the association was not statistically significant. This difference may be explained by the relatively low mortality in the present study, which is consistent with previous studies on Japanese patients.\textsuperscript{26} The lower mortality in Japanese patients is thought to be because of the lower prevalence of ischemic pathogenesis as a cause of heart failure in this population. Furthermore, there was a trend toward better survival in PVR+ patients of the HFrEF cohort; however, WRF itself was still not a significant predictor of cardiac mortality in either of the patient groups. The association between WRF and the prognosis in patients with heart failure was a complicated and context-dependent issue. For example, a recent study showed that WRF induced by initiating renin–angiotensin–aldosterone system inhibitors was associated with a poor prognosis in those with HFpEF, not with HFrEF.\textsuperscript{27} In another study, although WRF was established as a predictor of poor prognosis in patients, the association was less evident in patients with HFpEF.\textsuperscript{1} The diversity in the causes of WRF and the pathology of heart failure may explain these findings. The key in elucidating the association between WRF and the prognosis of patients with heart failure lies in a future analysis based on the classification of WRF stratified by the reasons for WRF and the pathological background characteristics of patients such as HFpEF or HFrEF. From the findings of our analysis, we think that PVR solely causes WRF in HFpEF, and this may provide more information for further understanding the complex association between WRF and the prognosis in patients.

**Study Limitations**

The present study has some limitations. First, it is based on data from an observed registry. Furthermore, the relatively small number of patients limits the statistical power of the findings. A prospective confirmation and the analysis of a larger, more diverse population are needed. Second, we estimated the intravascular volume using the ideal body weight method.\textsuperscript{28} Although this method was validated in both healthy volunteers and in patients with heart failure,\textsuperscript{9} changes in the ratio of intravascular volume to body weight, which are likely to occur during AHF treatment, may modify the results. Therefore, in future studies, PV needs to be evaluated more precisely using scintigraphy or bioimpedance analysis. Third, we were not able to analyze the dose and duration of diuretic therapy because of the lack of data. Considering that previous observational findings showed that a high dose of diuretics was associated with WRF in patients with AHF, estimating the effect of diuretic dose escalation on WRF in HFpEF will be an important task in the future. Finally, we empirically defined the PVR+ group as the top tertile of estimated PVR rate according to previous studies on hemoconcentration.\textsuperscript{24} A clinically relevant estimated PVR cutoff value for avoiding WRF needs to be defined in the future.

**Conclusions**

Estimated PVR during hospitalization is a predictor of WRF in HFpEF but not in HFrEF. Aggressive decongestion with diuretics may lead to WRF in patients with HFpEF in whom congestion is mainly caused by the redistribution of body fluid rather than volume overload.

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**Disclosures**

None.

**References**

Body fluid control by diuresis is the fundamental treatment of acute heart failure. Although diuresis is essential for relieving the symptoms associated with acute heart failure, its excess can lead to the worsening of renal function (WRF), which is a common complication encountered during hospitalization for acute heart failure. The main underlying mechanism of WRF is thought to be related to a plasma volume reduction (PVR) with a subsequent reduction in renal perfusion and activation of the renin–angiotensin–aldosterone system; therefore, maintenance of the optimal plasma volume without the resultant impairment of renal function is essential. In the present study, we estimated the PVR during hospitalization for acute heart failure in patients with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). An excess of estimated PVR was found to be associated with WRF in the HFpEF group but not in the HFrEF group. This difference may reflect the pathophysiological difference between HFpEF and HFrEF. In HFpEF, the volume distribution was the predominant cause of congestion rather than volume overload, which is typically the main cause of congestion in HFrEF. In addition, diuretics were more frequently used in patients with excessive PVR. These findings imply that PVR caused by diuresis can trigger WRF more easily in HFpEF than in HFrEF. Because the information available on diuretic therapy optimization in HFpEF is limited, it may be a rational treatment strategy to consider in excessive PVR caused by diuresis for preventing subsequent WRF in HFpEF.
Effect of Estimated Plasma Volume Reduction on Renal Function for Acute Heart Failure Differs Between Patients With Preserved and Reduced Ejection Fraction

Makoto Takei, Shun Kohsaka, Yasuyuki Shiraishi, Ayumi Goda, Yuki Izumi, Mayuko Yagawa, Atsushi Mizuno, Mitsuaki Sawano, Taku Inohara, Takashi Kohno, Keiichi Fukuda and Tsutomu Yoshikawa
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