Effect of Estimated Plasma Volume Reduction on Renal Function for Acute Heart Failure Differs Between Patients With Preserved and Reduced Ejection Fraction

Takei et al: Plasma Volume Reduction and Renal Function

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Abstract

Background—The prognostic relevance of plasma volume reduction (PVR) in acute heart failure patients (AHF) 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 (WET-HF) Registry were examined. The plasma volume (PV) 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 AHF patients, 181 (47.5%) had heart failure with preserved ejection fraction (HFPEF). Estimated PVR was associated with worsening renal function (WRF) in the HFPEF (odds ratio (OR) = 3.28, 95% confidence interval (CI) = 1.55–6.96, P = 0.002) but not in the heart failure with reduced ejection fraction (HFREF) cohort (OR = 1.22, 95% CI = 0.61–2.42, P = 0.57). This association in the HFPEF cohort remained significant after adjusting for a history of hypertension and diabetes and the estimated glomerular filtration rate (OR = 3.34, 95% CI = 1.52–7.33, P = 0.003). The use of intravenous diuretics was a significant predictor of PVR in the HFPEF and HFREF groups.

Conclusions—The effect of estimated PVR differs by HF type, and the estimated PVR during hospitalization is a predictor of WRF in HFPEF but not in HFREF patients.

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

Key Words: heart failure, renal function, diastolic heart failure, diuretics, plasma
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 (CKD), and the use of diuretics as predictors of WRF in patients requiring AHF hospitalization \(^1\).

In particular, the use of diuretics leading to WRF has received considerable clinical attention \(^1\,^3\,^5\). 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 PV without the resultant impairment of renal function is essential for AHF management.

Since AHF is a heterogeneous condition, the impact of PVR may differ depending on AHF subclasses based on ejection fraction. Abramov et al. reported that patients with heart failure with preserved ejection fraction (HFPEF) had a lower total blood volume (i.e., the intravascular volume) than those with heart failure with reduced ejection fraction (HFREF) \(^9\). Similarly, Schwartzenberg et al. reported a greater stroke volume reduction in HFPEF than
HFREF after vasodilation treatment, indicating the presence of occult intravascular hypovolemia in HFPEF. Therefore, we aimed to compare the effect of PVR on renal function during AHF hospitalization between HFPEF and HFREF patients from the West Tokyo Heart Failure (WET-HF) Registry.

Methods

Study Design

Data from the WET-HF Registry, which was obtained between January 2007 and August 2014, were retrospectively analyzed. The WET-HF 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 two university hospitals and two 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 WET-HF Registry, those with a recorded serum hemoglobin (Hb), serum creatinine (Cr), body weight at admission and discharge, and left ventricular ejection fraction (LVEF) data during hospitalization were included in this study.
The estimated glomerular filtration rate (eGFR), which was adjusted for age and sex, was calculated from the serum Cr in each patient. To minimize errors associated with the estimation of PV, patients with serum Hb levels ≤7 g/dL at admission (6 patients whose erythrocyte volumes were likely to change during hospitalization), eGFR <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; additionally, 8 patients who died during hospitalization were also excluded.

**Plasma Volume 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:

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

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 radiolabelled albumin. Additionally, we multiplied 1.31 to the estimated plasma volume from the ideal body weight method in HFREF and by 1.10 in HFPEF, according to a previous report that validated the ideal body weight method with radiolabelled albumin in both HFPEF and HFREF.

Patients in the top tertile of the estimated PVR rate were classified as the PVR+ group.

HFPEF patients were defined as AHF patients with LVEF of ≥40% at admission. WRF was defined as a ≥20% decrease in the eGFR during hospitalization.

In addition, patients in the top tertile of the hematocrit increase during hospitalization were defined as the hemoconcentration group. The association between hemoconcentration 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 due to heart failure, and myocardial infarction, was used as the primary endpoint for long-term prognosis.

Additionally, the association between WRF and cardiac mortality in the HFPEF and HFREF 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 means ± standard deviations. Ordinal variables were summarized using a median with 25 and 75 percentiles. The clinical characteristics of patients with and without estimated PVR in the HFPEF and HFREF groups were compared using Student’s t-test, Pearson’s chi-square test, and Mann-Whitney’s U test as appropriate. Univariate logistic regression analysis was performed to examine the association between the estimated PVR and WRF in the HFPEF and HFREF groups. Multivariable logistic regression analysis was used to adjust for known predictors of WRF among the AHF patients. 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, USA). A *P* value <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 HFPEF group (Figure). Table 1 shows the patients’ background characteristics according to the presence and absence of estimated PVR for each group (HFPEF and HFREF). Patients with preserved EF tended to be older (72.2 years vs. 66.6
years, $P < 0.001$) and were more frequently female (39.2% vs. 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 Plasma Volume Reduction**

Intravenous diuretics were more frequently used in the PVR+ group of the HFREF and HFPEF cohorts (Table 1). The PVR+ group also showed external edema on admission more frequently. In addition, Hb was significantly lower in the PVR+ patients than in the PVR− patients from the HFPEF group but not in the HFREF group. The absolute estimated PVR was not statistically different between HFPEF and HFREF, 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, and eGFR on admission (OR = 3.34,
95% CI: 1.52–7.33, \( P = 0.003 \); Table 2). We also analyzed the association between hemococoncentration and WRF. The association between hemococoncentration and WRF was again solely observed in 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 Plasma Volume Reduction**

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 HFPEF group, and were 2 (3.0%) and 12 (9.0%), respectively, in the HFREF 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.\textsuperscript{18, 19} In this study, diuretics were more frequently used in PVR+ patients than in PVR− patients. Further, 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 AHF patients. To achieve this goal, decongestion must maintain pace with plasma refilling from the extravascular space to the intravascular space.\textsuperscript{20} Previous studies have assessed intravascular volume loss on the basis of hemoconcentration.\textsuperscript{7, 8} 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 plasma volume reduction and WRF in HFPEF, which was
obtained from the estimated PVR and hemoconcentration, may imply the universality of our notion. Further, previous studies have focused on the association between elevated central venous pressure (CVP) and WRF. Theoretically, PVR leads to a reduction in CVP, but as shown previously, net-fluid loss does not predict this reduction and simply lowering the CVP 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 plasma volume must be carefully monitored when treating HFPEF patients 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 Hb, serum albumin, and serum total protein tend to develop hemoconcentration during AHF hospitalization. In the present study, patients with a lower Hb 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 HFPEF patients 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 over the past two decades, it is necessary to re-evaluate existing therapy. The information available regarding diuretic therapy optimization is limited, and no data available thus far indicate how to prevent WRF from developing in HFPEF patients. 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. 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. The lower mortality in Japanese patients is thought to be due to the lower prevalence of ischemic etiology as a cause of heart failure in this population. Further, 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. In another study, although WRF was established as a
predictor of poor prognosis in patients, the association was less evident in patients with
HFPEF. 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
heart failure patients 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 believe 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 observational
registry. Further, 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 by using the ideal body weight method. Although this method was validated in both healthy volunteers and in patients with heart failure, 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 by using scintigraphy or bio-impedance 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 AHF patients, estimating the effect of diuretic dose escalation on WRF in HFPEF will be an important task in the future. Lastly, we empirically defined the PVR+ group as the top tertile of estimated PVR rate according to previous studies on hemoconcentration. 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 HFPEF patients in whom congestion is mainly caused by the redistribution of body fluid rather than volume overload.
Sources of Funding

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Disclosures

None.

References


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Table 1. Patients’ background characteristics according to the presence/absence of plasma volume reduction (PVR) in the heart failure with preserved ejection fraction (HFPEF) and heart failure with reduced ejection fraction (HFREF) cohorts

<table>
<thead>
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<th>HFPEF</th>
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<td></td>
<td>PVR</td>
<td>non-PVR</td>
<td>P value</td>
<td>PVR</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age</td>
<td>74.0 ± 12.0</td>
<td>71.3 ± 13.7</td>
<td>0.19</td>
<td>65.1 ± 16.2</td>
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<td>Sex (% male)</td>
<td>53.3</td>
<td>65.5</td>
<td>0.12</td>
<td>76.1</td>
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<td>3, 2, 4</td>
<td>3, 2, 3</td>
<td>0.11</td>
<td>3, 3, 4</td>
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<tr>
<td>Length of hospital stay (days)</td>
<td>14.7 ± 6.4</td>
<td>15.3 ± 6.3</td>
<td>0.59</td>
<td>15.5 ± 5.6</td>
</tr>
<tr>
<td>Medical History</td>
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<td>HTN (%)</td>
<td>61.0</td>
<td>59.3</td>
<td>0.83</td>
<td>50.0</td>
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<td>DM (%)</td>
<td>35.0</td>
<td>30.5</td>
<td>0.54</td>
<td>36.4</td>
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<td>Echocardiographic parameters</td>
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<tr>
<td>Ischemic etiology (%)</td>
<td>15.0</td>
<td>24.0</td>
<td>0.16</td>
<td>23.9</td>
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<td>CKD (%)</td>
<td>38.3</td>
<td>34.7</td>
<td>0.63</td>
<td>41.8</td>
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<tr>
<td>LVEF (%)</td>
<td>55.6 ± 8.4</td>
<td>55.1 ± 8.5</td>
<td>0.72</td>
<td>30.0 ± 6.3</td>
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<td>LVDD (mm)</td>
<td>47.8 ± 8.1</td>
<td>48.2 ± 6.9</td>
<td>0.73</td>
<td>58.9 ± 8.4</td>
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<tr>
<td>LVDs (mm)</td>
<td>32.4 ± 6.8</td>
<td>32.9 ± 7.0</td>
<td>0.67</td>
<td>49.5 ± 9.3</td>
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<tr>
<td>LAAd (mm)</td>
<td>44.3 ± 9.3</td>
<td>45.6 ± 11.8</td>
<td>0.46</td>
<td>46.0 ± 8.0</td>
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<td>IVC d (mm)</td>
<td>13.9 ± 0.39</td>
<td>16.0 ± 0.47</td>
<td>0.66</td>
<td>17.3 ± 0.46</td>
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Laboratory data on admission

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<td>Serum Cr (mg/dL)</td>
<td>1.05 ± 0.54</td>
<td>1.15 ± 0.62</td>
<td>0.27</td>
<td>1.19 ± 0.47</td>
<td>1.18 ± 0.54</td>
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<td>Hb (mg/dL)</td>
<td>11.6 ± 2.1</td>
<td>12.7 ± 2.4</td>
<td>0.003</td>
<td>13.0 ± 2.4</td>
<td>13.2 ± 2.2</td>
<td>0.59</td>
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<td>Serum Na (mEq/L)</td>
<td>139.5 ± 5.16</td>
<td>139.6 ± 3.66</td>
<td>0.88</td>
<td>139.9 ± 3.53</td>
<td>139.6 ± 4.89</td>
<td>0.66</td>
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<tr>
<td>Serum BNP (pg/mL)</td>
<td>565.2 ± 568.7</td>
<td>594.4 ± 604.8</td>
<td>0.76</td>
<td>827.2 ± 506.1</td>
<td>1027 ± 1032</td>
<td>0.14</td>
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Physical examination on admission

20
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<tr>
<th></th>
<th>62.1</th>
<th>48.2</th>
<th>0.09</th>
<th>70.3</th>
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<td>JVD (%)</td>
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<td>External edema (%)</td>
<td>85.0</td>
<td>57.8</td>
<td>&lt;0.001</td>
<td>83.6</td>
<td>52.0</td>
<td>&lt;0.001</td>
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<td>SIII (%)</td>
<td>58.3</td>
<td>51.7</td>
<td>0.40</td>
<td>75.8</td>
<td>67.7</td>
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**Treatment**

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<th></th>
<th>70.0</th>
<th>52.9</th>
<th>0.03</th>
<th>68.2</th>
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<tr>
<td>ACEI (%)</td>
<td>16.7</td>
<td>11.8</td>
<td>0.09</td>
<td>22.4</td>
<td>31.6</td>
<td>0.57</td>
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<td>ARB (%)</td>
<td>30.0</td>
<td>43.0</td>
<td>0.09</td>
<td>22.5</td>
<td>33.8</td>
<td>0.17</td>
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<tr>
<td>β blocker (%)</td>
<td>33.6</td>
<td>38.3</td>
<td>0.72</td>
<td>49.2</td>
<td>58.3</td>
<td>0.23</td>
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**Plasma volume estimation**

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<tr>
<th></th>
<th>15.9 ± 4.8</th>
<th>1.3 ± 7.3</th>
<th>&lt;0.001</th>
<th>14.8 ± 5.4</th>
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<td>PVR rate (% of plasma volume on admission)</td>
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<td>Absolute PVR (mL)</td>
<td>486.5 ± 187.8</td>
<td>50.8 ± 184.0</td>
<td>&lt;0.001</td>
<td>528.3 ± 220.8</td>
<td>49.7 ± 206.8</td>
<td>&lt;0.001</td>
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<tr>
<td>Absolute PVR per hospital day (mL/day)</td>
<td>40.1 ± 27.2</td>
<td>2.2 ± 31.5</td>
<td>&lt;0.001</td>
<td>38.5 ± 20.1</td>
<td>3.8 ± 20.5</td>
<td>&lt;0.001</td>
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Values are expressed as mean ± standard deviation for variables with normal distributions and as a median (interquartile range) for variables with non-normal distribution.

HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; PVR, plasma volume reduction; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL/min; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular diameter; LVDs, systolic left ventricular diameter; LAd, left atrial diameter; IVCd, inferior vena cava diameter; Cr, creatinine; Hb, hemoglobin; Na, sodium; BNP, brain natriuretic peptide; JVD, jugular vessel dilatation; SIII, third heart sound; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Table 2. Logistic regression analysis models for predicting worsening renal failure

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<td>HFREF</td>
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<td>HFPEF</td>
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<td>OR</td>
<td>95% CI</td>
<td>P value</td>
<td>OR</td>
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<td>P value</td>
<td>OR</td>
<td>95% CI</td>
<td>P value</td>
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<td>1.55–6.96</td>
<td>0.002</td>
<td>1.22</td>
<td>0.61–2.42</td>
<td>0.57</td>
<td>3.34</td>
<td>1.52–7.33</td>
<td>0.003</td>
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<td>0.74–3.24</td>
<td>0.24</td>
<td>1.03</td>
<td>0.56–2.69</td>
<td>0.42</td>
<td>1.02</td>
<td>1.00–1.03</td>
<td>0.03</td>
</tr>
<tr>
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<td>0.99–1.05</td>
<td>0.18</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.47</td>
<td>1.83</td>
<td>0.78–4.32</td>
<td>0.17</td>
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<tr>
<td>HTN</td>
<td>1.68</td>
<td>0.77–3.69</td>
<td>0.19</td>
<td>3.74</td>
<td>1.73–8.10</td>
<td>0.001</td>
<td>1.71</td>
<td>0.76–3.86</td>
<td>0.20</td>
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<tr>
<td>DM</td>
<td>1.80</td>
<td>0.84–3.86</td>
<td>0.13</td>
<td>0.89</td>
<td>0.44–1.79</td>
<td>0.74</td>
<td></td>
<td></td>
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<tr>
<td>eGFR</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.02</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.34</td>
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</table>

PVR, plasma volume reduction; HTN, hypertension; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; OR, odds ratio; CI, confidence interval
Figure Legend

Figure. Study population

WET-HF, Western Tokyo Heart Failure Registry; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; PVR, plasma volume reduction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin
WET-HF
January 1, 2007-August 31, 2014
n = 381

Exclusion
- Hb on admission \( \leq 7 \text{ g/dL} \) n = 6
- GFR < 15 mL/min n = 22
- Hospitalization \( \geq 30 \text{ days} \) n = 63
- In-hospital death n = 8

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