Urine Sodium Excretion After Tolvaptan Administration Is Dependent Upon Baseline Serum Sodium Levels

A Possible Explanation for the Improvement of Hyponatremia With Scarce Chance of Hypernatremia by a Vasopressin Receptor Antagonist

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Summary

Several studies have demonstrated that tolvaptan (TLV) can improve hyponatremia in advanced heart failure (HF) patients with rare chance of hypernatremia. However, changes in serum sodium concentrations (S-Na) in patients with or without hyponatremia during TLV treatment have not been analyzed.

Ninety-seven in-hospital patients with decompensated HF who had received TLV at 3.75-15 mg/day for 1 week were enrolled. Among 68 “responders”, who had achieved any increases in urine volume (UV) during the first day, urinary sodium excretion during 24 hours (U-NaEx24) increased significantly during one week of TLV treatment along with higher baseline S-Na (P < 0.05 and r = 0.325). Considering a cut-off value (S-Na, 132 mEq/L; AUC, 0.711) for any increases in U-NaEx24, we defined “hyponatremia” as S-Na < 132 mEq/L. In hyponatremic responders (n = 25), S-Na increased significantly, although 1 week was not sufficient for normalization (125.8 ± 5.0 versus 128.9 ± 4.3 mEq/L, P < 0.05), along with unchanged U-NaEx24 (2767 ± 2703 versus 2972 ± 2950 mg/day, NS). In contrast, in normonatremic responders (n = 43), S-Na remained unchanged (136.6 ± 3.1 versus 137.4 ± 2.9 mEq/L, NS) along with increased U-NaEx24 (2201 ± 1644 versus 4198 ± 3550 mg/day, P < 0.05).

TLV increased S-Na only in hyponatremic responders by way of pure aquaresis, but increased U-NaEx24 only in normonatremic responders, which explains the scarcity of hypernatremia. Epithelial Na-channels in the distal nephrons, whose repression by TLV increases urinary sodium excretion, may be attenuated by reduced ATP-supply in worse hemodynamics under hyponatremia. (Int Heart J 2014; 55: 131-137)

Key words: Heart failure, Vasopressin, Urine osmolality

The orally active vasopressin antagonists vaptans provide potential effects to treat chronic water-retaining disorders. Among them, the vasopressin type 2 (V2) receptor antagonist tolvaptan (TLV) has been available for patients with heart failure (HF) with symptomatic congestion or hyponatremia. TLV has been demonstrated to ameliorate congestion, stabilize hemodynamics, and improve renal function without any significant adverse effects. We also reported the efficacy and safety of TLV in (1) amelioration of congestion even in stage D HF patients and (2) improvement of renal function by converting ongoing diuretics to TLV.

With respect to serum sodium concentration (S-Na), various studies in Europe and the United States have demonstrated the efficacy of TLV to improve hyponatremia with little chance of hypernatremia, ie, S-Na > 145 mEq/L (eg, 1.7% of hypernatremia in the EVEREST study and 0% in the QUEST study). In Japan, we can administer TLV to HF patients to treat their congestion regardless of baseline S-Na as long as hypernatremia or rapid increases in S-Na do not develop. However, no studies have examined the efficacy and safety of TLV in patients with normonatremia thus far. Therefore, we have analyzed and compared the effect of TLV on S-Na between patients with and without hyponatremia.

Methods

Study design and patients: Of the patients who were hospitalized for decompensated HF at the University of Tokyo Hospital between February 2011 and May 2013, consecutive 97 pa-
tients who received 3.75-15 mg/day of TLV on a de novo basis for more than 1 week were retrospectively analyzed. The initial dose of TLV was determined by the attending physician taking into consideration the hemodynamics and degree of congestion of the patient, and was maintained during the study period.

Eligible patients had either lower limb edema, pulmonary congestion, or jugular venous distension due to fluid retention despite receiving tolerable amounts of conventional diuretics that included loop diuretics and/or thiazides, in addition to appropriate restriction of sodium and water intake. All patients had one or more previous hospitalizations due to decompensated HF during the past 12 months. All patients were assigned to New York Heart Association (NYHA) class III or IV.

Patients were excluded and did not receive TLV if they had hypovolemia, severe stenotic valvular disease, severe systemic infection or inflammation, end-stage renal failure on hemodialysis, acute coronary syndrome within 1 month, or hypernatremia with S-Na > 145 mEq/L. Patients who were dependent on any mechanical supports such as ventilator assist devices, intra-aortic balloon pumping, extracorporeal membranous oxygenation, mechanical ventilation, or any combination of these devices, were also excluded.

During the study period, restrictions on water intake were loosened according to the weight loss of the patients, but salt restriction was continued at 6 g/day (equivalent to 2.4 g/day of sodium). Patients with impaired consciousness who lacked a sense of thirst were also excluded from this study. Concomitant use of intravenous agents including human atrial natriuretic peptide, phosphodiesterase III inhibitors, dobutamine, or dopamine as well as i.v. furosemide was continued if present, and the doses were not changed during the study period.

The present study complied with the Declaration of Helsinki and the institutional review board of University of Tokyo approved the research protocol [the application number, 779(1)]. Informed consent was obtained from all patients before enrollment.

### Measures:

The following variables were collected (1) < 24 hours before the introduction of TLV and (2) at 1 week after the administration of TLV: demographic characteristics; blood laboratory parameters; and symptom parameters due to HF. Echocardiographic parameters were obtained < 24 hours before the administration of TLV by using a standard, comprehensive M-mode and 2D echocardiogram by expert echo-cardiologists. Left ventricular ejection fraction was calculated using the biplane Simpson method from apical 4- and 2-chamber views. No patient underwent urinary catheter placement, but daily UV was measured during the study period. Urine samples were obtained (1) in the early morning just before the administration of any medication including TLV and other diuretics on day 1, (2) at 4 hours after the administration of TLV on day 1, and (3) in the early morning just before the administration of any medication including TLV on day 7. Estimated amount of urinary sodium excretion during 24 hours (U-NaEx24) was calculated by the following formula, i.e. [U-NaEx24 (mg/day)] = 2.3 × [urinary sodium concentration (U-Na) (mg/dL)] × [predicted amount of urinary creatinine excretion during 24 hours (mg/day)] / [urinary creatinine concentration (mg/dL)]. Predicted amounts of urinary creatinine excretion during 24 hours were calculated in males and females separately by the following formula, i.e. (1) for males, 15.12 × [body weight (kg)] + 7.39 × [body height (cm)] - 12.63 × [age (years)] -79.9, and (2) for females, 8.58 × [body weight (kg)] + 5.09 × [body height (cm)] -4.72 × [age (years)] -74.9.

Patients in whom UV on day 1 accomplished an increase compared with that of day 0 were defined as “responders” to TLV and the reverse as “non-responders”, as we previously demonstrated its validity and reliability in association with various clinical parameters including amelioration of congestion. Patients with impaired consciousness who lacked a sense of thirst were also excluded from this study. Concomitant use of intravenous agents including human atrial natriuretic peptide, phosphodiesterase III inhibitors, dobutamine, or dopamine as well as i.v. furosemide was continued if present, and the doses were not changed during the study period.

The present study complied with the Declaration of Helsinki and the institutional review board of University of Tokyo approved the research protocol [the application number, 779(1)]. Informed consent was obtained from all patients before enrollment.

### Statistical analysis:

Categorical parameters are presented as frequencies and percentages, and continuous variables as the mean ± standard deviation. The patient characteristics were compared using the unpaired t-test or Mann-Whitney test for continuous variables, and the chi-square test or Fisher’s exact test for categorical variables as appropriate. Pearson’s product-moment correlation coefficient was also calculated to assess the relations between baseline parameters and changes in U-NaEx24. The cut-off value of the baseline sodium concentration for any increases in urine sodium excretion during the one week of TLV treatment was analyzed by ROC analyses. S-Na and U-NaEx24 measured on day 7 were compared with those of baseline by the Wilcoxon signed-rank test.

All statistical tests were 2-tailed, with P < 0.05 regarded as being statistically significant. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA).

### Results

**Baseline characteristics of responders to TLV (Table 1):**

Among 97 patients with decompensated HF who were enrolled in the present study, 68 (70.1%) were responders with increased UV at day 1 compared with day 0. Among all 68 responders, TLV was initiated at 13 days after patient admission on average. Nine patients (13.2%) had ischemic etiology, and 27 (39.7%) had been diagnosed with dilated cardiomyopathy. All patients, unless contraindicated, had received standard medical therapy for HF that included β-blockers (91.2%), and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (82.4%) at the maximum tolerable doses. All patients had been dependent on a type of diuretic, including furosemide (mean, 61.9 ± 37.3 mg/day; range, 20-240 mg/day), spironolactone (32.9 ± 22.3 mg/day; 0-100 mg/day), and trichlormethiazide (0.4 ± 0.8 mg/day; 0-4 mg/day). Thirty-one patients (45.6%) were dependent on continuous infusion of...
catecholamine. Many of the enrolled responders had mild end-organ dysfunction; the mean serum creatinine concentration was 1.3 ± 0.5 mg/dL and the mean serum total bilirubin concentration was 1.5 ± 1.9 mg/dL. S-Na averaged 132.6 ± 6.5 mEq/L and the range was 112-144 mEq/L. No patient had hyponatremia with S-Na > 145 mEq/L before the administration of TLV as per the exclusion criteria. Plasma arginine vasopressin was detectable in all patients (mean, 5.2 ± 3.1 pg/mL; range, 1.5-13.9 pg/mL) despite their relatively lower levels of serum osmolality (276.3 ± 13.3 mOsm/L). Thirteen patients (19.1%) had preserved left ventricular systolic function with an ejection fraction ≥ 50%. Baseline U-NaEx24 was approximately zero-balanced with sodium intake (~2.5 g/day).

Changes in S-Na and urinary sodium excretion in responders after one week of TLV treatment: The correlations between changes in U-NaEx24 during one week of TLV treatment and baseline parameters are shown in Table II. The changes in U-NaEx24 had no significant correlation with baseline parameters except S-Na (P = 0.011, r = 0.325) (Figure 1). The cut-off value of S-Na for any increase in U-NaEx24 was 132 mEq/L (area under curve, 0.711; sensitivity, 0.769; specificity, 0.572). We defined hyponatremia as S-Na < 132 mEq/L based on this result.

As for the comparison between the hyponatremic and normonatremic groups (Table I), hyponatremic responders had a slight but significantly greater decompensated state, higher serum level of total bilirubin, higher plasma levels of arginine vasopressin and B-type natriuretic peptide, a lower left ventricle diastolic diameter, and a lower ejection fraction ≥ 50%.

Table I. Demographic, Laboratory, and Echocardiographic Parameters Before the Administration of TLV in Responders With and Without Hyponatremia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 68)</th>
<th>Serum sodium concentration &lt; 132 mEq/L (n = 25)</th>
<th>Serum sodium concentration ≥ 132 mEq/L (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic parameters</td>
<td></td>
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</tr>
<tr>
<td>Dose of TLV, mg daily</td>
<td>6.3 ± 3.8</td>
<td>6.0 ± 3.2</td>
<td>6.5 ± 4.2</td>
<td>0.580</td>
</tr>
<tr>
<td>Timing of TLV administration, day</td>
<td>13 (4-144)</td>
<td>12 (4-144)</td>
<td>15 (4-140)</td>
<td>0.264</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.9 ± 18.9</td>
<td>44.3 ± 19.9</td>
<td>53.1 ± 17.6</td>
<td>0.061</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>46 (67.6)</td>
<td>20 (80.0)</td>
<td>26 (60.5)</td>
<td>0.097</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.0 ± 4.0</td>
<td>22.0 ± 3.6</td>
<td>22.0 ± 4.3</td>
<td>0.984</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>58.6 ± 13.8</td>
<td>59.2 ± 11.3</td>
<td>58.3 ± 15.1</td>
<td>0.805</td>
</tr>
<tr>
<td>Etiology of ischemia, n (%)</td>
<td>9 (13.2)</td>
<td>5 (20.0)</td>
<td>4 (9.3)</td>
<td>0.209</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>94.2 ± 9.5</td>
<td>92.1 ± 10.4</td>
<td>98.4 ± 9.8</td>
<td>0.185</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>83.4 ± 9.4</td>
<td>85.4 ± 9.4</td>
<td>81.4 ± 10.4</td>
<td>0.243</td>
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<tr>
<td>Concomitant medication</td>
<td></td>
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<td></td>
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<tr>
<td>Furosemide, mg daily</td>
<td>61.9 ± 37.3</td>
<td>70.4 ± 40.9</td>
<td>57.0 ± 34.5</td>
<td>0.154</td>
</tr>
<tr>
<td>Spironolactone, mg daily</td>
<td>32.9 ± 22.3</td>
<td>39.0 ± 22.9</td>
<td>29.4 ± 21.4</td>
<td>0.088</td>
</tr>
<tr>
<td>Trichlormethiazide, mg daily</td>
<td>0.4 ± 0.8</td>
<td>0.6 ± 1.2</td>
<td>0.3 ± 0.5</td>
<td>0.136</td>
</tr>
<tr>
<td>Number of prescribed diuretics</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td>0.154</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>62 (91.2)</td>
<td>23 (92.0)</td>
<td>39 (90.7)</td>
<td>0.614</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>56 (82.4)</td>
<td>20 (80.0)</td>
<td>36 (83.7)</td>
<td>0.698</td>
</tr>
<tr>
<td>Catecholamine infusion, n (%)</td>
<td>31 (45.6)</td>
<td>19 (76.0)</td>
<td>12 (27.9)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>132.6 ± 6.5</td>
<td>125.8 ± 5.0</td>
<td>136.6 ± 3.1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.1 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>0.340</td>
</tr>
<tr>
<td>Serum BUN, mg/dL</td>
<td>32.8 ± 15.2</td>
<td>33.2 ± 19.6</td>
<td>32.5 ± 12.3</td>
<td>0.874</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>0.506</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.5 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>3.4 ± 0.5</td>
<td>0.532</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>1.5 ± 1.1</td>
<td>1.8 ± 0.9</td>
<td>1.3 ± 1.1</td>
<td>0.045*</td>
</tr>
<tr>
<td>Serum osmolality, mOsm/L</td>
<td>276.3 ± 13.3</td>
<td>263.8 ± 12.9</td>
<td>283.2 ± 7.3</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Plasma arginine vasopressin, pg/mL</td>
<td>5.2 ± 3.1</td>
<td>8.1 ± 4.0</td>
<td>4.7 ± 2.3</td>
<td>0.038*</td>
</tr>
<tr>
<td>Plasma BNP, log_{10} pg/mL</td>
<td>2.8 ± 0.4</td>
<td>2.9 ± 0.3</td>
<td>2.7 ± 0.5</td>
<td>0.013*</td>
</tr>
<tr>
<td>Urine parameters</td>
<td></td>
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<tr>
<td>Urine volume of day 0, mL/day</td>
<td>1337 ± 357</td>
<td>1300 ± 332</td>
<td>1305 ± 372</td>
<td>0.350</td>
</tr>
<tr>
<td>U-OSM, mOsm/L</td>
<td>490.6 ± 151.5</td>
<td>466 ± 141</td>
<td>505 ± 157</td>
<td>0.310</td>
</tr>
<tr>
<td>U-sodium, mEq/L</td>
<td>54.6 ± 29.5</td>
<td>48.0 ± 27.0</td>
<td>58.4 ± 30.6</td>
<td>0.160</td>
</tr>
<tr>
<td>U-potassium, mEq/L</td>
<td>32.0 ± 15.3</td>
<td>32.0 ± 16.7</td>
<td>32.0 ± 14.6</td>
<td>0.992</td>
</tr>
<tr>
<td>U-urea nitrogen, mg/dL</td>
<td>756.2 ± 302.1</td>
<td>761.0 ± 312.9</td>
<td>753.7 ± 300.8</td>
<td>0.933</td>
</tr>
<tr>
<td>U-creatinine, mg/dL</td>
<td>95.9 ± 59.9</td>
<td>93.5 ± 64.4</td>
<td>97.1 ± 58.1</td>
<td>0.819</td>
</tr>
<tr>
<td>Estimated U-sodium excretion, mg/24 hours</td>
<td>2002 ± 2245</td>
<td>2767 ± 2703</td>
<td>2200 ± 1643</td>
<td>0.375</td>
</tr>
<tr>
<td>FE_{Na}, %</td>
<td>0.77 ± 0.77</td>
<td>0.91 ± 1.09</td>
<td>0.70 ± 0.5</td>
<td>0.410</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
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<tr>
<td>LV diastolic diameter, mm</td>
<td>61.4 ± 11.7</td>
<td>62.4 ± 7.1</td>
<td>60.8 ± 13.5</td>
<td>0.581</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>30.0 ± 18.9</td>
<td>22.3 ± 9.2</td>
<td>33.9 ± 21.2</td>
<td>0.008*</td>
</tr>
<tr>
<td>Ejection fraction ≥ 50% n (%)</td>
<td>13 (19.1)</td>
<td>0 (0)</td>
<td>13 (30.2)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure symptom score</td>
<td>6.4 ± 1.4</td>
<td>6.9 ± 1.3</td>
<td>6.1 ± 1.4</td>
<td>0.013*</td>
</tr>
<tr>
<td>NYHA class IV, n (%)</td>
<td>31 (45.6)</td>
<td>18 (72.0)</td>
<td>13 (30.2)</td>
<td>0.001†</td>
</tr>
</tbody>
</table>

TLV indicates tolvaptan; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; U-OSM, urine osmolality; U, urinary; FENa, fractional excretion of sodium; LV, left ventricle; and NYHA, New York Heart Association. *P < 0.05 by unpaired t-test or Mann-Whitney test as appropriate. †P < 0.05 by chi-square test or Fisher’s exact test as appropriate.
tricular ejection fraction, and more frequent requirement for inotrope infusion. Baseline U-Na, U-NaEx24, and FENa were not different between the two groups.

TLV treatment increased S-Na significantly in hyponatremic responders (n = 25), whereas S-Na remained unchanged in normonatremic responders (n = 43) (Figure 2). U-NaEx24 increased significantly in normonatremic responders, but remained unchanged in hyponatremic responders after one week of TLV treatment (Figure 3).

Clinical course in hyponatremic and normonatremic responders: Clinical parameters obtained at 4 hours after the administration of TLV on day 1 and day 7 were compared in hyponatremic and normonatremic groups. U-Na concentration obtained at 4 hours after the administration of TLV was significantly higher in normonatremic responders than that in hyponatremic responders (Table III). Urine osmolality was equally decreased compared with baseline in both the normonatremic and hyponatremic groups at 4 hours after TLV treatment.

On day 7, U-NaEx24 was significantly higher in the normonatremic responders than in the hyponatremic responders (Table IV). U-NaEx24 was increased by approximately 2-fold in the normonatremic responders, which means they had a minus balance since their food contained ~2.5 g/day of sodium.

As for the changes in HF parameters on day 7, serum total bilirubin, plasma B-type natriuretic peptide, and body weight exhibited better improvement in normonatremic than in hyponatremic responders (Table IV). As a result, hyponatremic responders still had higher serum concentrations of total bilirubin and higher concentrations of plasma B-type natriuretic peptide (Table IV). The serum potassium level was slightly increased on day 7 in the normonatremic responders compared with the hyponatremia responders (Table IV).

Effects of TLV in nonresponders: In the nonresponders (n = 29), S-Na remained unchanged during the study period regard-

### Table II. Correlation Between Changes in U-NaEx24 During 1 Week of TLV Treatment and Baseline Parameters in Responders. Versus Changes in U-NaEx24 During 1 Week of TLV Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
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<tbody>
<tr>
<td>Demographic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose of TLV, mg daily</td>
<td>0.274</td>
<td>0.145</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.463</td>
<td>0.097</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.331</td>
<td>0.129</td>
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<tr>
<td>Body weight, kg</td>
<td>0.098</td>
<td>0.218</td>
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<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide, mg daily</td>
<td>0.710</td>
<td>-0.049</td>
</tr>
<tr>
<td>Spironolactone, mg daily</td>
<td>0.846</td>
<td>0.026</td>
</tr>
<tr>
<td>Trichlormethiazide, mg daily</td>
<td>0.428</td>
<td>0.105</td>
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<tr>
<td>Laboratory parameters</td>
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<tr>
<td>Serum sodium, mEq/L</td>
<td>0.011*</td>
<td>0.325</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>0.546</td>
<td>-0.080</td>
</tr>
<tr>
<td>Serum BUN, mg/dL</td>
<td>0.190</td>
<td>-0.173</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.927</td>
<td>-0.012</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>0.522</td>
<td>0.085</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>0.143</td>
<td>-0.193</td>
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<tr>
<td>Serum osmolality, mOsm/L</td>
<td>0.198</td>
<td>0.170</td>
</tr>
<tr>
<td>Plasma arginine vasopressin, pg/mL</td>
<td>0.634</td>
<td>-0.113</td>
</tr>
<tr>
<td>Plasma BNP, log10 pg/mL</td>
<td>0.869</td>
<td>-0.022</td>
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<tr>
<td>Echocardiographic parameters</td>
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<tr>
<td>LV diastolic diameter, mm</td>
<td>0.924</td>
<td>0.015</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>0.533</td>
<td>-0.094</td>
</tr>
</tbody>
</table>

U-NaEx24 indicates urinary sodium excretion during 24 hours; TLV, tolvaptan; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; and LV, left ventricle. *P < 0.05 by Pearson’s product-moment correlation coefficient.
less of the baseline serum sodium level (normonatremic group, 136.5 ± 3.8 versus 135.4 ± 4.6 mEq/L; hyponatremic group, 125.6 ± 4.0 versus 126.4 ± 3.1 mEq/L, P = 0.428 and P = 0.645, respectively, by paired t-test). In the same manner, there were no statistically significant changes in U-NaEx24 during the study period in nonresponders (normonatremic; 3120 ± 2478 versus 2410 ± 1788 mg/day, hyponatremic; 3084 ± 2806 versus 2500 ± 1610 mg/day, P = 0.265 and P = 0.385, respectively, by paired t-test).

**Discussion**

In the present study, we demonstrated that hyponatremia improved at 1 week after the administration of TLV in responders, whereas such an improvement was not observed at all in nonresponders. Hypernatremia was not observed in any participants. U-NaEx24 increased significantly on day 7 only in normonatremic responders.

Patients with advanced HF are often complicated with severe congestion refractory to considerable amounts of diuretics, which favors the development of hyponatremia by enhanced sodium excretion and increases in a variety of neurohormonal secretions.18 In Europe and the United States, many authors have previously reported the advantage of TLV in amelioration of such hyponatremia, which results in not only disturbance of consciousness but also poor prognosis.7,19,20 As we reported,14,15,21 the efficacy of TLV is limited to responders. Nonresponders are associated with reduced concentrating and diluting ability of urine probably due to dysfunction of the collecting ducts and/or loss of the medullar osmotic gradient.14,21 Consistently, nonresponders had a larger amount of estimated sodium excretion in urine together with higher FENa at baseline, which indicated nephrogenic renal dysfunction.

Thus far, there have been no reports discussing the administration of TLV in HF patients with normonatremia, probably due to the fact that TLV has not been approved for HF patients with normonatremia in Europe and the United States.

### Table III. Urine Parameters at 4 Hours After TV Initiation in Responders With and Without Hyponatremia

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 68)</th>
<th>Serum sodium concentration &lt; 132 mEq/L (n = 25)</th>
<th>Serum sodium concentration ≥ 132 mEq/L (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U-OSM, mOsm/L</td>
<td>276.8 ± 97.0</td>
<td>255 ± 111</td>
<td>289 ± 87</td>
<td>0.157</td>
</tr>
<tr>
<td>U-sodium after 4 hour, mEq/L</td>
<td>52.7 ± 30.3</td>
<td>48.0 ± 27.0</td>
<td>58.4 ± 30.6</td>
<td>0.001*</td>
</tr>
<tr>
<td>U-potassium after 4 hour, mEq/L</td>
<td>25.9 ± 15.2</td>
<td>26.8 ± 14.9</td>
<td>25.3 ± 15.5</td>
<td>0.703</td>
</tr>
<tr>
<td>U-urea nitrogen after 4 hour, mg/dL</td>
<td>330.9 ± 189.6</td>
<td>334.0 ± 234.4</td>
<td>329.4 ± 165.7</td>
<td>0.932</td>
</tr>
<tr>
<td>U-creatinine after 4 hour, mg/dL</td>
<td>39.8 ± 30.1</td>
<td>40.1 ± 32.8</td>
<td>39.6 ± 28.9</td>
<td>0.948</td>
</tr>
</tbody>
</table>

TLV indicates tolvaptan; U-OSM, urine osmolality; and U, urinary. *P < 0.05 by unpaired t-test or Mann-Whitney test as appropriate.

### Table IV. Characteristics at 1 Week After TLV Treatment in Responders With and Without Hyponatremia.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 68)</th>
<th>Serum sodium concentration &lt; 132 mEq/L (n = 25)</th>
<th>Serum sodium concentration ≥ 132 mEq/L (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>57.7 ± 13.4</td>
<td>57.9 ± 11.7</td>
<td>57.5 ± 14.5</td>
<td>0.903</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>134.1 ± 5.5</td>
<td>128.6 ± 4.3</td>
<td>137.4 ± 2.9</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>0.834</td>
</tr>
<tr>
<td>Serum BUN, mg/dL</td>
<td>28.7 ± 14.3</td>
<td>26.3 ± 14.0</td>
<td>30.0 ± 14.4</td>
<td>0.310</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.3 ± 0.6</td>
<td>1.1 ± 0.4</td>
<td>1.4 ± 0.7</td>
<td>0.074</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>1.6 ± 1.1</td>
<td>2.1 ± 1.0</td>
<td>1.2 ± 1.1</td>
<td>0.002*</td>
</tr>
<tr>
<td>Plasma BNP, log10 pg/mL</td>
<td>2.7 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>2.6 ± 0.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>Urine parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U-OSM, mOsm/L</td>
<td>367.5 ± 137.1</td>
<td>337.6 ± 142.5</td>
<td>383.4 ± 133.5</td>
<td>0.268</td>
</tr>
<tr>
<td>U-sodium, mEq/L</td>
<td>57.3 ± 31.2</td>
<td>53.2 ± 36.3</td>
<td>59.6 ± 28.2</td>
<td>0.491</td>
</tr>
<tr>
<td>U-potassium, mEq/L</td>
<td>25.9 ± 13.5</td>
<td>24.9 ± 11.9</td>
<td>26.5 ± 15.0</td>
<td>0.696</td>
</tr>
<tr>
<td>U-urea nitrogen, mg/dL</td>
<td>512.8 ± 320.3</td>
<td>450.6 ± 335.8</td>
<td>552.4 ± 298.7</td>
<td>0.360</td>
</tr>
<tr>
<td>U-creatinine, mg/dL</td>
<td>78.0 ± 54.8</td>
<td>75.5 ± 52.5</td>
<td>79.3 ± 56.6</td>
<td>0.826</td>
</tr>
<tr>
<td>Estimated U-sodium excretion, mg/24 hours</td>
<td>3730 ± 3608</td>
<td>2972 ± 2950</td>
<td>4198 ± 3550</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>FE&lt;sub&gt;Na&lt;/sub&gt;, %</td>
<td>1.13 ± 1.13</td>
<td>1.16 ± 1.22</td>
<td>1.11 ± 1.10</td>
<td>0.894</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure symptom score</td>
<td>4.5 ± 1.8</td>
<td>5.4 ± 1.7</td>
<td>4.0 ± 1.6</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

**Changes of clinical parameters**

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 68)</th>
<th>Serum sodium concentration &lt; 132 mEq/L (n = 25)</th>
<th>Serum sodium concentration ≥ 132 mEq/L (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>-1.24 ± 1.66</td>
<td>-0.87 ± 1.05</td>
<td>-1.45 ± 1.90</td>
<td>0.165</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>-0.08 ± 0.54</td>
<td>0.23 ± 0.94</td>
<td>-0.13 ± 0.65</td>
<td>0.248</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>0.06 ± 0.49</td>
<td>0.05 ± 0.41</td>
<td>0.16 ± 0.46</td>
<td>0.265</td>
</tr>
<tr>
<td>Plasma BNP, pg/mL</td>
<td>-154.1 ± 315.7</td>
<td>-167.2 ± 283.3</td>
<td>-144.1 ± 547.6</td>
<td>0.451</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen; BNP, B-type natriuretic peptide; U-OSM, urine osmolality; U, urinary; and FE<sub>Na</sub>, fractional excretion of sodium. *P < 0.05 by unpaired t-test or Mann-Whitney test as appropriate.
contrast, the Japanese government has approved TLV for use in normonatremic patients. Based on our experience, TLV treatment is highly effective for ameliorating congestion in normonatremic patients in clinical practice, although hypernatremia must be avoided. As shown in Figure 2, S-Na increased only in hyponatremic responders, whereas it remained unchanged in normonatremic responders. As a result, there were no patients who developed hypernatremia after the administration of TLV in our practice, including this study population.

Why did TLV treatment not increase S-Na in normonatremic responders? Congestion was effectively treated also in normonatremic responders as well as hyponatremic responders. We observed significant decreases in urine osmolality at 4 hours after the administration of TLV in both groups, which indicated sufficient aquaresis. Recently, it has been demonstrated that TLV enhances excretion of sodium in urine in addition to aquaresis as we previously discussed. 

Plasma arginine vasopressin stimulates reabsorption of sodium through activation of epithelial Na-channels (ENaC) in the distal nephrons. 

Inhibition of V2 receptors by TLV represses ENaC activity and may possibly increase excretion of sodium in urine. As shown in Figure 3, U-NaEx24 increased significantly after TLV treatment in normonatremic responders. The mechanism can be a safety net against hypernatremia after TLV treatment in normonatremic responders. The slight increase in serum potassium concentration in normonatremic responders can also be explained by ENaC inhibition by TLV. Although sodium intake is an important factor that determines sodium excretion, salt restriction was continued at 6 g/day during the study period in all in-hospital patients, and there were no differences in the amount of daily salt intake between the hyponatremic and normonatremic groups.

ENaC is an active transporter and may require a substantial energy supply. ENac is expressed in cortical collecting ducts, where ATP is normally abundant. In sharp contrast to normonatremic responders, we observed that U-NaEx24 remained unchanged in hyponatremic responders. Hemodynamic recovery was insufficient even after one week of TLV treatment in patients with hyponatremia (Table IV). ENaC activity may be attenuated by reduced ATP-supply due to such impaired circulation, and attenuated ENaC activity leads to a lesser response to TLV in terms of increases in sodium excretion. In contrast, ENaC activity may be more preserved due to the relatively higher supply of ATP under less impaired hemodynamics in the normonatremic group, and a higher amount of sodium is in turn excreted in urine after TLV administration.

Another reason why hypernatremia did not emerge during TLV treatment may be the enhanced natriuretic effect of concomitant diuretics due to amelioration of renal congestion by TLV. Patients with advanced HF are often refractory to conventional natriuretic agents owing to renal congestion, which recovers more easily in normonatremic patients because of their relatively stable hemodynamics. In contrast, volume overload may continue in patients with hyponatremia even after one week of TLV treatment considering insufficient recovery of body weight and serum total bilirubin concentration. The natriuretic effect of concomitant diuretics may still be repressed under persistent renal congestion in patients with hyponatremia.

We acknowledge that our study has several limitations.

1. It was conducted retrospectively in a single center, and consequently included a limited number of patients and might have patient selection bias. Doses of TLV were determined by attending physicians after determining the hemodynamic stability and degree of congestion of the patient.
2. We observed the clinical courses for 1 week after the administration of TLV under fixed doses of other medication including diuretics, and the improvement in hyponatremia was not sufficient. Longer administration of TLV along with reduction of concomitant natriuretic diuretics may better improve the hyponatremia. Resolution of hyponatremia has been reported to be associated with improved in-hospital and 1-year mortality. Longer prognosis under improved hyponatremia by TLV treatment would be a future concern.
3. In this study, TLV was initiated at almost 2 weeks after admission because we tried our best to optimize conventional treatment before the administration of TLV. Therefore, the results may not be adapted to patients in an acutely decompen-sated phase.
4. The formula to estimate UNaEx24 used in this study was originally developed from urine samples in a healthy population. Although we would like to validate the formula among patients with cardioenal failure or those who received diuretics, 24-hour urine collection is prohibited at many institutes, including our hospital, to avoid in-hospital infection. Our calculation, therefore, might not be accurate in terms of absolute values, although the trend of sodium excretion should still be valid.
5. We did not demonstrate direct involvement of ENaC or data on aldosterone concentration in the present study, although several previous reports demonstrated a significant relationship between TLV and ENaC in sodium excretion in urine. Further investigation of TLV and ENaC would be necessary.

In conclusion, we have demonstrated that TLV can improve hyponatremia only in responders, and that hypernatremia rarely emerges in patients with normonatremia by TLV treatment, which is explained by enhanced excretion of not only free water but also sodium, especially in patients with normonatremia. We believe that the above mechanism contributes to the safety of TLV when applied to normonatremic patients.

References


