Successful Treatment of Congestive Heart Failure Due to Severe Aortic Valve Stenosis With Low Dose Tolvaptan in Elderly Patients

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Summary

Medical therapy for severe aortic valve stenosis (AS) is necessary for inoperable patients due to comorbid conditions. Tolvaptan (TLV), unlike other diuretics, resulted in modest changes in filling pressures associated with an increase in urine output, suggesting that TLV improves congestive heart failure (CHF) due to severe AS without hemodynamic instability.

We retrospectively investigated 14 consecutive patients ≥ 80 years of age admitted due to decompensated CHF with severe AS at Juntendo University Hospital from April 2014 to November 2015. Seven of the 14 patients were treated with TLV. We examined the safety and efficacy of TLV treatment for severe AS.

Mean age was 90.0 ± 6.3 years and mean aortic valve area was 0.57 ± 0.22 cm^2. Urine volume at day 1 of TLV treatment was increased and urine osmolality significantly decreased at day 1 of TLV treatment (all $P < 0.05$). New York Heart Association classification and brain natriuretic peptide levels significantly improved 1 week after treatment and at discharge (all $P < 0.05$) whereas brain natriuretic peptide levels did not improve in the patients without TLV. Severe adverse events did not occur during TLV treatment. During the first 3 days, blood pressure and heart rate were relatively stable. TLV treatment did not affect serum creatinine, blood urea nitrogen, or the estimated glomerular filtration rate.

In elderly patients with severe AS, TLV treatment improved CHF without hemodynamic instability. Further prospective studies are needed to assess the safety and efficacy of TLV in decompensated heart failure due to severe AS. (Int Heart J 2017; 58: 1-7)

Key words: Worsening renal function, Diuretics, Acute decompensated heart failure, Hemodynamic stability, Coronary intensive care unit

Aortic valve stenosis (AS) is a progressive disease characterized by inadequate cardiac output, decreased exercise capacity, heart failure, or death from cardiovascular causes.[1)] The prevalence of calcific AS increases with age, which is found in approximately 9.8% of octogenarians.[2-5)] Furthermore, medical therapy has very little to offer to symptomatic patients with severe AS, and they usually need surgery.[6-8)] However, medical therapy may be needed as a bridge therapy in cases of transcatheter aortic valve implantation in inoperable patients due to comorbid conditions, including high age.[9)] Although diuretics are beneficial when there is abnormal accumulation of fluid, they must be used in patients with AS with caution because rapid progression of hypovolemia may induce lower cardiac output and critical hypotension.

Recently, tolvaptan (TLV) has been developed to treat patients with congestive heart failure.[10-17)] TLV has a specific feature of excreting only water without increasing electrolyte excretion because it functions as an antagonist to the vasopressin V2 receptor in renal collecting tubules.[18)] In addition, it has been shown that TLV treatment resulted in favorable but modest changes in filling pressures (ie, pulmonary capillary wedge pressure, right atrial pressure, and pulmonary artery pressure) associated with a significant increase in urine output.[19)] Therefore, TLV is a potential candidate for improving decompensated heart failure due to severe AS without hemodynamic instability. In this study, we investigated the safety and efficacy of TLV in 7 elderly patients with decompensated heart failure due to severe AS.

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Received for publication May 10, 2016. Revised and accepted October 8, 2016.

Released in advance online on J-STAGE May 23, 2017. (This is "Advance Publication".)

METHODS

Subjects: We retrospectively investigated 14 consecutive patients aged ≥ 80 years admitted to Juntendo University Hospital between April 2014 and November 2015 for decompensated congestive heart failure with severe AS. Seven patients were treated with TLV (the TLV group) and the remaining 7 were treated without TLV (the control group). All patients provided written consent, and study protocols were approved by the institutional review board. Demographic data, including age, sex, body weight, blood pressure, heart rate, New York Heart Association (NYHA) classification, and medication during hospitalization; laboratory data, including hemoglobin, sodium, albumin, renal function, liver function, and brain natriuretic peptide (BNP) levels; and comorbidities, including ischemic heart disease, atrial fibrillation, atrial flutter, hypertension, dyslipidemia, and diabetes mellitus were obtained from our medical records.

Echocardiography: Echocardiography was performed at admission, and severe AS was defined as follows: 1) aortic jet velocity ≥ 4 m/s, 2) mean systolic pressure gradient ≥ 40 mmHg in the presence of normal cardiac output, or 3) effective aortic orifice ≤ 1.0 cm^2.

Efficacy of TLV treatment: We examined daily urine volume for the first week in both groups, and plasma and urine osmolality for the first 3 days in the TLV group. We also estimated body weight, NYHA classification, and BNP levels before TLV treatment, at day 7, and at discharge.

Safety of TLV treatment: Occurrence of severe adverse events, including all-cause death, sudden cardiac death, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, and worsening of heart failure, during hospitalization was examined. For the first 3 days, blood pressure and heart rate were measured every 8 hours from initiation of TLV treatment. Serum concentrations of hemoglobin (Hb), hematocrit (Ht), sodium, potassium, creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), total bilirubin (T-bil), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (γ-GTP), total protein (TP), and albumin (Alb) before treatment, at day 7, and at discharge were also examined. Worsening renal function was defined as increases in serum creatinine ≥ 0.3 mg/dL from baseline to discharge.[20]

Statistical analysis: Continuous variables are expressed as the mean ± standard deviation (SD), and categorical variables as percentages. Statistical differences between the groups were analyzed by the Student *t*-test and chi-square test. The changes of continuous variables were analyzed using the paired *t*-test. The changes of NYHA classification were analyzed as a discrete variable using the Wilcoxon signed rank test. JMP (Version 5.0 for Windows, SAS Institute, Cary, NC, USA) was used for the statistical analyses, and P values < 0.05 were considered statistically significant.

RESULTS

Table I presents the characteristics of the study patients at baseline. In the TLV group, mean age was 90.0 ± 6.3 years, and mean body mass index was 21.1 ± 4.5 kg/m^2. Before TLV treatment, all patients, except patient #4, had been treated with other diuretics (ie, furosemide, azosemide, and spironolactone). Carperitide, a vasodilator, was used by patients #1 and 4. Inotropic agents were used by patients #3, 4, and 5. Patients #5 and 6 had consumed beta-blockers, and patients #1 and 7 had consumed ARBs. The mean dose of TLV was relatively low (4.8 ± 1.8 mg daily). The mean treatment period was 9.4 ± 6.2 days (range: 3–21). The doses of TLV were not increased dur-

Table I. Baseline Characteristics of Study Patients

Patient #	1	2	3	4	5	6	7	Controls (n = 7)
Gender	F	M	F	F	F	M	M	F/M 6/1
Age (years)	89	94	97	80	93	94	83	89 ± 5
BMI (kg/m^2)	21.8	20	18.9	29.4	14.3	21.1	22.3	24.51 (2.7)
NYHA class	4	4	3	4	4	4	4	3.9 (0.4)
Nohria-Stevenson	B	B	B	C	B	B	B	B/C 7/0
Clinical scenario	1	2	2	2	2	2	2	1.7 (0.5)
Previous ADHF	N	Y	N	N	N	N	N	Y/N 3/4
Hypertension	Y	N	Y	N	N	Y	Y	Y/N 6/1
Diabetes mellitus	Y	N	N	N	N	N	N	Y/N 2/5
Dyslipidemia	Y	N	N	N	N	Y	N	Y/N 4/3
AF/AFL	N	N	Y	N	Y	N	Y	Y/N 4/4
IHD	N	N	N	N	N	N	N	Y/N 2/5
Medication								
Tolvaptan (mg/day)	3.75	3.75	3.75	7.5	7.5	3.75	3.75	Y/N 0/7**
Other diuretics								
Furosemide	20mg iv	5mg iv	NA	NA	40mg po	20mg iv	20mg po	Y/N 6/1
Azosemide	NA	NA	60mg po	NA	30mg po	NA	NA	Y/N 5/2
Spironolactone	NA	25mg po	25mg po	NA	25mg po	NA	NA	Y/N 4/3
Inotropic agents	NA	NA	Digoxin	Dopa	Pimo	NA	NA	Y/N 0/7*
Vasodilator	Carp	NA	NA	Carp	NA	NA	NA	Y/N 2/5
Beta blocker	NA	NA	NA	NA	Biso	Meto	NA	Y/N 0/7
ACE-I/ARB	Tel	NA	NA	NA	NA	NA	Tel	Y/N 5/2

BMI indicates body mass index; NYHA, New York Heart Association; ADHF, acute decompensated heart failure; AF/AFL, atrial fibrillation/atrial flutter; IHD, ischemic heart disease; Dopa, dopamine; Pimo, pimobendan; Carp, carperitide, Biso bisoprolol; Meto, metoprolol; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, and Tel, telmisartan. *P < 0.05 and **P < 0.01 TLV treatment versus Controls.

ing the treatment period. In all patients, the reason for discontinuation of TLV treatment was improvement of heart failure, as assessed by their physician. There were no significant differences in the characteristics of study patients between the TLV group and the control group. Compared to the control group, the TLV group used more inotropic agents.

Table II shows the results of echocardiography at baseline. The mean aortic valve area, mean flow velocity, mean pressure gradient, mean ejection fraction, mean E/e' ratio, and mean estimated right ventricle pressure were 0.57 ± 0.22 cm^2, 4.6 ± 0.27 m/s, 47.7 ± 5.4 mmHg, 59.6 ± 8.1%, 21.7 ± 11.3 m/s, and 42.8 ± 13.0 mmHg, respectively. Compared to the control group, the TLV group had higher aortic jet velocity and mean systolic pressure gradient.

Efficacy of TLV treatment: As shown in Figure 1A, compared with the day before TLV treatment (day 0: 44 ± 23 mL/hour), the urine volume at days 1 and 2 was increased (day 1: 60 ± 27 mL/hour, $P = 0.005$; day 2: 63 ± 23 mL/hour, $P = 0.054$) in the TLV group, but it remained unchanged (day 0: 60 ± 27 mL/hour, day 1: 60 ± 27 mL/hour, day 2: 63 ± 23 mL/hour) in the control group. Compared with day 0, there were no differences in the urine volumes at days 3–6 in both the TLV and control groups. Urine osmolality significantly decreased from day 0 to day 1 of TLV treatment (from 401 ± 132 to 271 ± 145 mL, $P = 0.02$; Figure 1B), whereas serum osmolality did not change for the first 3 days of TLV treatment. Mean NYHA classification at day 0 was 3.9 ± 0.4, and it was significantly improved 1 week after TLV treatment and at discharge (1 week: 2.6 ± 0.5, $P = 0.031$; discharge: 2.6 ± 0.5, $P = 0.016$; Figure 2A left). Additionally, NYHA classification improved 1 week after treatment and at discharge in the control group (day 0: 3.9 ± 0.4; 1 week: 2.4 ± 0.5, $P = 0.016$; discharge: 2.4 ± 0.5, $P = 0.016$; Figure 2A right). Compared with the mean body weight at day 0 (46.4 ± 11.3 kg), the values decreased 1 week after TLV treatment and at discharge (1 week: 45.1 ± 11.7 kg, $P = 0.16$; discharge: 43.2 ± 11.1 kg, $P = 0.002$; Figure 2B left). In the control group, body weight significantly decreased 1 week after treatment, but did not improve at discharge (day 0: 52.6 ± 3.7 kg; 1 week: 46.3 ± 9.8, $P = 0.048$; discharge: 46.7 ± 9.6, $P = 0.059$; Figure 2B right). BNP levels at day 0 were 1003 ±

Table II. Echocardiogram Data of Study Patients

Patient #	1	2	3	4	5	6	7	Mean (SD)	Controls (n = 7)
LVDd (mm)	51	48	44	50	43	46	40	46.0 (4.0)	46.1 (7.4)
LVDs (mm)	37	34	33	35	30	27	26	31.7 (4.2)	30.1 (7.6)
IVS (mm)	12	11	11	12.5	9	11	15	11.6 (1.8)	11.0 (1.8)
PW (mm)	12	11	12	12	12	11	14	12.0 (1.0)	10.1 (1.5)
LVEF (%)	54	57	49	60	57	73	67	59.6 (8.1)	58.7 (13.8)
AV flow velocity (m/s)	4.8	4.6	4.5	4.7	4.9	4.1	4.4	4.6 (0.3)	3.9 (0.4)*
Mean systolic PG (mmHg)	51	52	45	47	54	40	42	47.7 (5.4)	35.1 (9.4)*
AVA (cm^2)	0.36	0.40	0.40	0.80	0.40	0.80	0.80	0.57 (0.22)	0.61 (0.14)
AVAI (cm^2/m^2)	0.26	0.27	0.34	0.55	0.38	0.55	0.48	0.40 (0.12)	0.42 (0.05)
MR (grade)	mild	mild	moderate	mild	moderate	mild	trivial	NA	mild/moderate 3/2
E/e' ratio	14.8	14.8	27	28	42	10.2	14.7	21.7 (11.3)	19.5 (7.7)
Estimated RVP (mmHg)	64.5	36	46	36	41	52	24	42.8 (13.0)	35.0 (11.9)
IVC (mm)	23	12	19	18	15	17	14	16.9 (3.6)	14.7 (2.9)

LVDd indicates left ventricular end-diastolic diameter; LVDs, left ventricular end systolic diameter; IVS, interventricular septum; PW, posterior wall; LVEF, left ventricular ejection fraction; AV, aortic valve; AVA, aortic valve area; AVAI, aortic valve area index; MR, mitral valve regurgitation; RVP, right ventricular pressure; and IVC, inferior vena cava; *$P < 0.05$ TLV treatment versus controls.

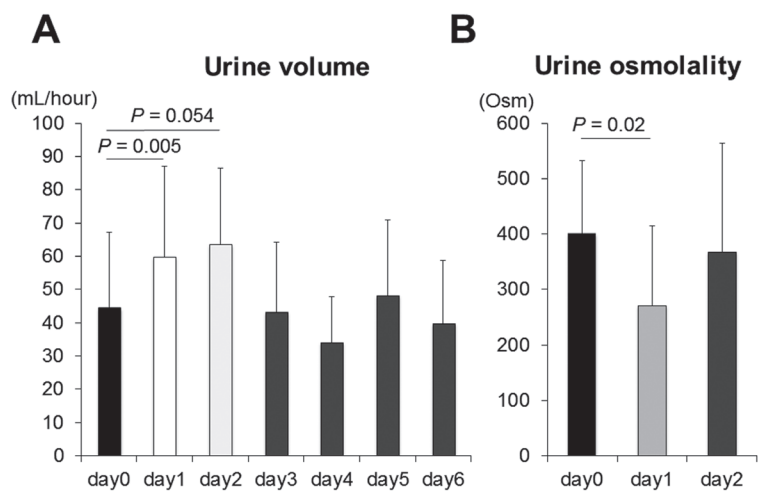

Figure 1. Changes of urine volume and urine osmolality after TLV treatment. Compared with the day before TLV treatment, the urine volume at days 1 and days 2 was increased. Compared with day 0, there were no significant differences in the urine volumes at days 3-6 (**A**). Urine osmolality significantly decreased from day 0 to day 1 of TLV treatment (**B**).

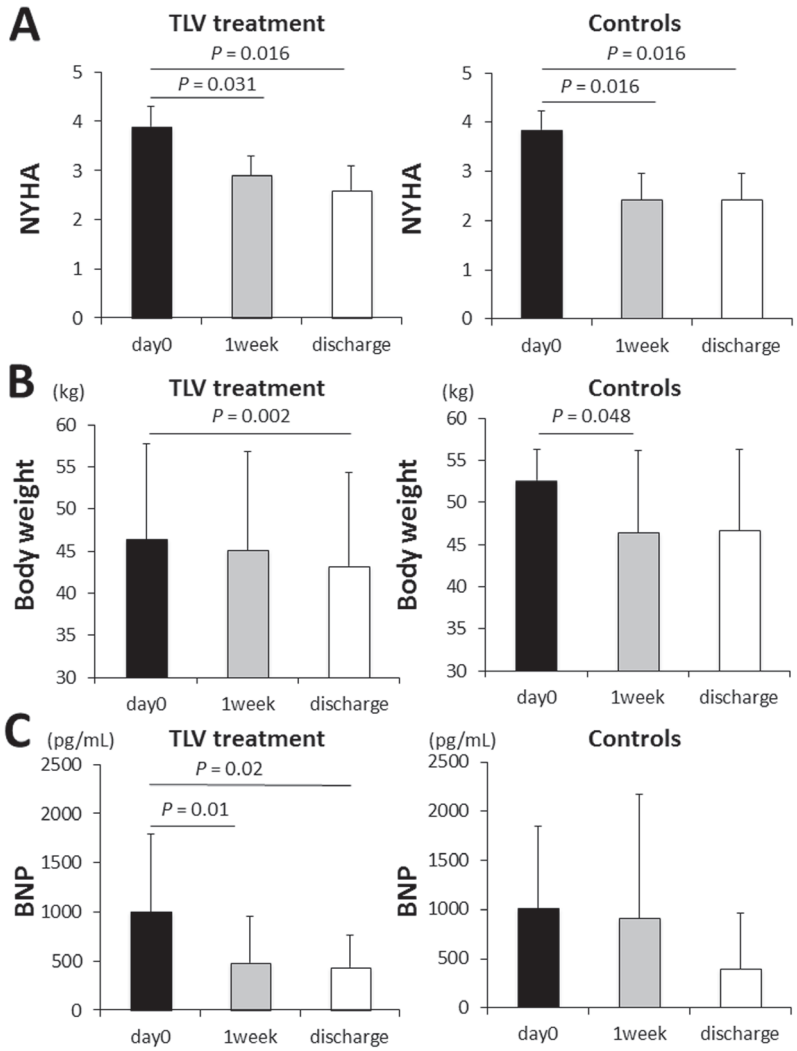

Figure 2. Changes of NYHA classification, body weight, and BNP levels after TLV treatment. NYHA classification significantly improved in the TLV and control groups (**A**). The mean body weight decreased at discharge in the TLV group and decreased 1 week after treatment in the control group (**B**). BNP levels decreased 1 week after TLV treatment and at discharge, whereas BNP levels did not improve in the control group (**C**).

789 pg/mL, which decreased 1 week after TLV treatment and at discharge (1 week: 481 ± 468 pg/mL, $P = 0.01$; discharge: 439 ± 327 pg/mL, $P = 0.02$; Figure 2C left), whereas BNP levels in the control group did not improve at 1 week after TLV treatment and at discharge (day 0: 1005 ± 839 pg/mL; 1 week: 909 ± 1258 pg/mL, $P = 0.60$; discharge: 399 ± 589 pg/mL, $P = 0.09$; Figure 2C right).

Safety of TLV treatment: Severe adverse events did not occur in the TLV group. In the control group, one patient received transcatheter aortic valve implantation. During the first 3 days, systolic and diastolic blood pressures every 8 hours were relatively stable than before TLV treatment (Figure 3). However, patients experienced increased heart rate after TLV treatment. The mean heart rate at 56 and 64 hours after initiation of TLV treatment was significantly higher relative to the baseline rate ($P = 0.03$ and 0.04, Figure 3). In the control group, systolic and diastolic blood pressures and heart rate did not change significantly. TLV treatment did not affect Hb, Ht, sodium, potassium, serum creatinine, BUN, eGFR, T-bil, AST, ALT, and γ-GTP levels during the study period, whereas the control group showed increased Hb and Ht levels 1 week after treatment and increased potassium level at discharge. TP and Alb levels increased after TLV treatment, although the control group had slightly decreased TP and Alb levels (Table III). Only patient #3 in the TLV group met the criteria of worsening renal function at discharge.

Discussion

To the best of our knowledge, this is the first study to examine the efficacy and safety of low-dose TLV treatment for patients with acute decompensated heart failure, particularly elderly patients, with severe AS. We showed that low-dose TLV is a candidate for treatment of heart failure accompanied by severe AS.

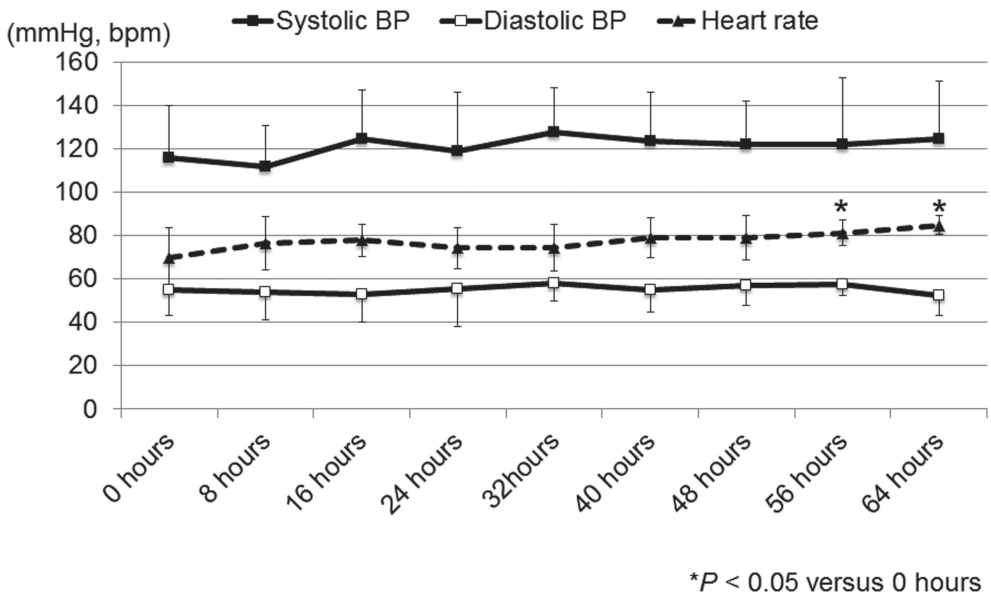

Figure 3. Changes of blood pressure and heart rate after TLV treatment. During the first 3 days, systolic and diastolic blood pressures at every 8 hours were relatively stable, whereas patients experienced increased heart rate after TLV treatment.

Table III. Changes of Laboratory Data at Baseline, 1 Week After Treatment, and Discharge

	TLV treatment (n = 7)			Controls (n = 7)		
	Baseline	1 week	Discharge	Baseline	1 week	Discharge
Hb (mg/dL)	10.0 (1.6)	10.0 (1.6)	10.5 (2.0)	11.0 (2.1)	12.4 (1.2)†	11.8 (1.9)
Ht (%)	30.1 (5.3)	32.0 (5.5)	31.3 (5.5)	33.0 (5.9)	38.9 (2.8)*†	36.5 (5.6)
Sodium (mEq/L)	136.3 (3.6)	139.3 (2.7)	137.4 (3.6)	140.3 (4.2)	144.3 (5.8)	140.4 (2.4)
Potassium (mEq/L)	4.6 (0.5)	4.5 (0.7)	4.4 (0.5)	3.7 (0.5)	3.9 (0.7)	4.1 (0.3)*
Creatinine (mg/dL)	1.26 (0.74)	1.17 (0.61)	1.12 (0.58)	0.94 (0.46)	0.76 (0.29)	0.69 (0.19)
eGFR (mL/minute/1.73m^2)	43.8 (21.5)	47.2 (24.2)	49.9 (24.2)	56.1 (29.1)	63.3 (22.2)	65.1 (12.8)
T-bil (mg/dL)	0.70 (0.19)	0.57 (0.17)	0.61 (0.16)	0.95 (0.51)	1.03 (0.39)†	0.73 (0.37)
AST (mg/dL)	19.7 (5.2)	18.6 (3.9)	19.3 (4.2)	32.0 (25.3)	32.3 (23.4)	18.9 (2.3)
ALT (mg/dL)	11.7 (4.6)	9.6 (3.2)	10.4 (3.1)	15.4 (5.9)	16.6 (7.3)†	13.1 (5.4)
γ-GTP (mg/dL)	22.7 (5.9)	23.7 (5.6)	18.9 (2.3)	24.4 (13.6)	25.7 (10.6)	20.1 (10.2)
TP (mg/dL)	5.5 (0.8)	5.9 (0.9)	6.2 (0.7)*	6.5 (0.7)†	6.3 (0.2)	6.0 (0.4)
Alb (mg/dL)	3.1 (0.5)	3.1 (0.3)	3.5 (0.4)*	3.5 (0.5)	3.1 (0.2)	2.9 (0.6)

Hb indicates hemoglobin; Ht, hematocrit; eGFR, estimated glomerular filtration rate; T-bil, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; γ-GTP, gamma-glutamyl transpeptidase; TP, total protein; and Alb, albumin. $^{*}P < 0.05$ and $^{**}P < 0.01$ Baseline versus Follow-up, $^{\dagger}P < 0.05$ TLV treatment versus controls.

Medical treatment for severe AS has not been established because most diuretics and vasodilators induce rapid progression of hypovolemia, which cause lower cardiac output and critical hypotension. In this study, however, TLV did not affect blood pressure, only modestly increased heart rate, and significantly increased urine output even in elderly patients with severe AS. TLV treatment improved symptoms and BNP levels and reduced body weight safely, whereas the BNP levels in the control group did not improve. Additionally, the control group showed increased Hb and Ht levels 1 week after treatment, which may indicate temporal hemoconcentration. TLV acutely produces free-water diuresis and an increase in serum osmolality, which have beneficial effects on the oncotic forces leading to tissue congestion. These effects produce a sustained movement of fluid from the extravascular to the vascular space without hemodynamic instability.[10,18] A clinical study showed that 15–60 mg doses of tolvaptan resulted in modest but favorable changes in filling pressures (ie, pulmonary capillary wedge pressure, right atrial pressure, and pulmonary artery pressure) that can be associated with a significant increase in urine output in patients with heart failure.[19] These effects differ from those of loop diuretics, in which a rapid reduction in intravascular volume pressure diminishes intracapillary hydrostatic pressure but has no effect on oncotic pressure.[10,18] This mechanism may work to preserve hemodynamic stability in patients with severe AS.

Both chronic kidney disease and worsening renal function are independent predictors of poor outcomes in patients with acute decompensated heart failure.[21-24] All study patients, except patient #3, did not show changes in serum creatinine, BUN, and eGFR levels during TLV treatment. In some studies, favorable effects for renal function of tolvaptan, unlike loop diuretics, have been reported in both *in vitro* and *in vivo* investigations.[25,26] Compared with furosemide, tolvaptan induced

aquaresis without compromising renal function or activating the sympathetic nervous system and renin–angiotensin–aldosterone system in a canine model of heart failure.[27] In an open-label, randomized, placebo-controlled crossover trial, tolvaptan caused aquaresis without decreasing renal blood flow or increasing plasma renin activity and serum aldosterone, which are both components of the renin–angiotensin–aldosterone system in patients with heart failure.[28] TLV has effects on the renin–angiotensin–aldosterone and sympathetic nervous system that are quite different from those of loop diuretics, which may preserve renal function in elderly patients with severe AS.

In patients with euvolemic and hypervolemic hyponatremia, TLV was effective in increasing serum sodium concentration.[29,30] In this study, serum sodium levels increased but not significantly during TLV treatment. Although the precise mechanism(s) remains unknown, low-dose and short-term TLV treatment may be preferable from the point of view of sodium metabolism.

Several patients took a very low dose (3.75 mg) of TLV as an initial dose, as determined by their physicians. Because this study was retrospective, we could not assess the reasons why their physicians determined the initial dose of TLV. However, this low-dose TLV was effective and safe for the elderly patients with severe AS. Therefore, low-dose TLV could be used as the initial treatment for these patients with hemodynamic instability, although the efficacy and safety of high-dose TLV remain unclear.

This was a retrospective observational study with a small sample size. Therefore, we could not evaluate the direct effects of TLV treatment on congestive heart failure after exclusion of the effects from standard therapy. Further prospective studies will be needed to clarify the efficacy of low-dose TLV in patients with severe AS. In this study, all patients showed preserved ejection fraction and systolic blood pressure > 100 mmHg at baseline. Therefore, the efficacy and safety of TLV treatment in patients with low cardiac output is uncertain. Furthermore, we do not have the precise infusion and intake volume data, which affects intravascular volume. However, the effects of infusion and intake volume may be limited because all study patients were admitted due to severe congestive heart failure and received a small amount of infusion and intake volume. In addition, we examined both body weight and urine volume daily. These data suggested that TLV treatment increased urine volume and decreased body weight regardless of the infusion and intake volume.

Conclusions: In elderly patients with severe AS, TLV treatment increased urine volume and decreased body weight, which resulted in improvements in patients who experienced heart failure without causing hemodynamic instability. Further prospective studies are needed to assess the safety and efficacy of TLV in the treatment of decompensated heart failure due to severe AS.

Disclosures

Dr. Daida and Dr. Miyauchi have received speakers' Bureau/Honorariums from Otsuka Pharmaceutical Co., Ltd. and Sanofi-Aventis K.K. Dr. Takagi and Dr. Miyazaki have received speakers' Bureau/Honorariums from Otsuka Pharmaceutical Co., Ltd. Dr. Kasai has received a speakers' Bureau/Honorarium from Otsuka Pharmaceutical Co., Ltd. and unrestricted research funding from Philips Respironics, Teijin Home Healthcare, and Fukuda Denshi. The remaining authors report no conflicts.

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