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ORIGINAL ARTICLE

Clinical safety and efficacy of tolvaptan for acute phase therapy in patients with low-flow and normal-flow severe aortic stenosis

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Abstract
Conventional diuretic therapy for low-flow (LF) severe aortic stenosis (SAS) often has an inadequate effect or causes hemodynamic instability. Tolvaptan is used for acute heart failure in addition to conventional diuretics, and it does not cause intravascular dehydration. This study aimed to retrospectively investigate the safety and efficacy of tolvaptan in the acute phase in 56 consecutive patients with SAS and compared LF-SAS with normal-flow (NF) SAS. The primary endpoints were adverse clinical events (death, worsening heart failure, worsening renal failure, fatal arrhythmia, cardiogenic or hypovolemic shock, and use of inotropic agents) and the volume of urine within 48 h of tolvaptan administration. Among 56 patients, 16 had LF-SAS (29%), and 40 had NF-SAS (71%). Severe adverse clinical events were not observed 48 h after tolvaptan administration. In both groups, the urine volume significantly increased after tolvaptan administration in comparison to 24 h before tolvaptan administration (both, $p < 0.01$). There were no changes in the urine volume during the initial 24 and 48 h. In the LF-SAS group, tolvaptan resulted in a significant decrease in fluid balance during the initial 24 and 48 h compared to 24 h before tolvaptan administration ($p < 0.05$). Adding tolvaptan to conventional treatment is safe and effective without renal dysfunction and hypotension in patients with SAS, including those with LF.

Keywords Tolvaptan · Severe aortic stenosis · Low-flow severe aortic stenosis · Normal-flow severe aortic stenosis

Introduction

In the aging society, the proportion of patients with aortic stenosis (AS) is increasing [1]. When AS progresses to severe AS (SAS), hospitalization because of acute decompensated heart failure (ADHF) is inevitable. Medical therapy such as diuretics is still necessary for those patients to improve symptoms or serve as bridge therapy to surgical aortic replacement or transcatheter aortic valve implantation (TAVI). However, clinicians generally use diuretics cautiously in patients with SAS because they are likely to induce cardiogenic shock due to the progression of intravascular hypovolemia [2]. In recent years, low-flow (LF) SAS has been considered difficult to diagnose, and is associated with a worse prognosis than normal-flow (NF) SAS [3]. LF-SAS is associated with a poor outcome even after TAVI, and the LF status itself is an independent prognostic marker of cardiovascular death [4, 5]. Patients with LF-SAS are more susceptible to intravascular hypovolemia because of a reduced cardiac output status after using diuretics [3].

Tolvaptan, a vasopressin-2 antagonist, has been reported to be effective and safe for use as a heart failure therapy in patients with ADHF [6, 7]. Tolvaptan leads to the loss of free water, and compared with loop diuretics, does not cause intravascular dehydration [8]. Thus, tolvaptan is more appropriate for use in ADHF patients with intravascular hypovolemia than other diuretics [9–11]. In addition, a previous study has reported that tolvaptan is safe and effective for use in elderly patients with ADHF due to SAS [2].

In this study, we hypothesized that tolvaptan would be a suitable therapy for heart failure with LF-SAS and NF-SAS. Thus, we investigated the clinical safety and efficacy of tolvaptan in patients with LF-SAS who were admitted because of ADHF. We then compared patients with NF-SAS to those with LF-SAS.

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Materials and methods

Study population

This retrospective observational study screened 250 consecutive patients who were hospitalized because of worsening ADHF (New York Heart Association (NYHA) class ≥ II) and were newly introduced to tolvaptan in a single cardiovascular center between June 2011 and December 2016. Patients who had no SAS and those with mild AS and moderate AS (aortic valve area > 1.0 cm^2) were excluded. Patients with SAS were retrospectively divided into LF-SAS and NF-SAS groups according to the stroke volume index determined by Doppler transthoracic echocardiography (LF-SAS group, stroke volume index < 35 mL/m^2; NF-SAS group, stroke volume index ≥ 35 mL/m^2), which was taken in the echo laboratory after transfer to the general ward from the intensive care unit [12].

Treatment and data collection

The treatment and data collection protocols are shown in Fig. 1. All patients were treated with the appropriate dose of diuretics required for ADHF before starting tolvaptan treatment. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which explain how to treat patients with ADHF using diuretics, were followed [13]. The initiation and dose of oral tolvaptan (3.75 or 7.5 mg once a day) were decided upon and started on day 2 of admission or on a later day after discussion among members of the heart team considering with patient's age or weight. We retrospectively evaluated the patients' clinical background characteristics; medications where the dose of furosemide was converted to an oral dose; standard two-dimensional B-mode and Doppler echocardiographic parameters, which were measured according to the American Society of Echocardiography guidelines [14, 15]; blood pressure; urine volume (before tolvaptan administration and 24 and 48 h after tolvaptan administration); and laboratory data (before tolvaptan administration and 48 h after tolvaptan administration).

Study endpoints

The primary endpoints were adverse clinical events (death, worsening heart failure, worsening renal failure, fatal arrhythmia, cardiogenic or hypovolemic shock vital, and use of inotropic agents) to evaluate the safety of tolvaptan, and the volume of urine (per 24 h) and fluid balance (per 24 h) to assess the efficacy of tolvaptan 48 h after tolvaptan initiation. The secondary endpoints were changes in blood pressure; serum sodium, potassium, and creatinine levels; estimated glomerular filtration rate (eGFR); hematocrit; serum blood urea nitrogen (BUN); and albumin level 48 h after tolvaptan initiation compared with baseline. In addition, each endpoint was compared between the LF-SAS and NF-SAS groups.

Statistical analysis

Continuous variables were assessed for the normal distribution using the Shapiro–Wilk test. Data with a normal distribution were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) (IQR, 25–75th percentiles). The differences in normally and non-normally distributed data between the two groups were compared using the t-test and Mann–Whitney test, respectively. The Chi square test was used to compare categorical variables, which are expressed as numbers and percentages. Additionally, the clinical adverse events and outcomes at 48 h after tolvaptan treatment initiation were compared between the two groups. Statistical analyses were performed using SPSS, version 24.0 (IBM, Armonk, NY, USA) and MedCalc software, version 17.5.5 (MedCalc Software, Ostend, Belgium); $p < 0.05$ was considered statistically significant.

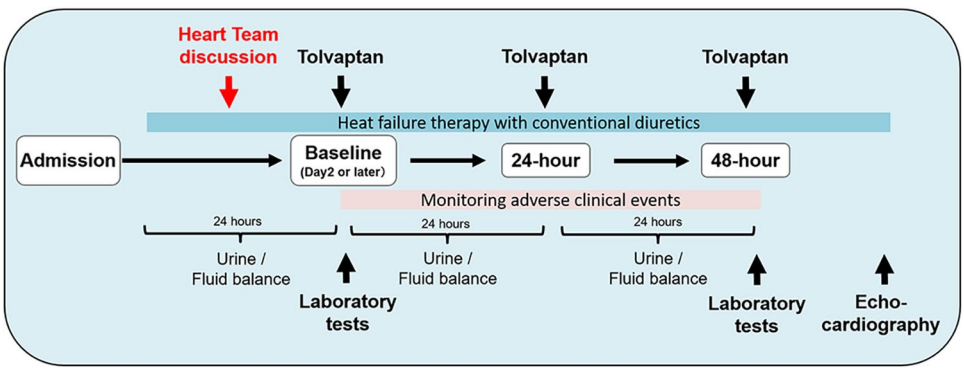

Fig. 1 Treatment and data collection protocols

Results

Among 250 consecutive patients, 194 patients were excluded due to no evidence of SAS, such as ischemic heart disease ($n=85$), cardio-myocardiopathy ($n=49$), other valvular heart disease ($n=47$), arrhythmia ($n=9$), adult congenital heart disease ($n=2$), and pulmonary hypertension ($n=2$). A total of 56 patients were diagnosed with SAS. Baseline characteristics are shown in Table 1. The median age was 84 years (interquartile range 80–87 years), and 37.5% were men. Among the 56 included patients, 16 (28.6%) were diagnosed with LF-SAS and 40 (71.4%) were diagnosed with NF-SAS. All patients with SAS had symptoms indicating an NYHA class ≥ III. The incidence of chronic kidney disease was significantly higher among patients with NF-SAS than in patients with LF-SAS ($p<0.05$). There was no significant

Table 1 Clinical background characteristics, echocardiographic parameters, and laboratory data at baseline

	All patients ($n=56$)	LF-SAS group ($n=16$)	NF-SAS group ($n=40$)	p value
Clinical background characteristics				
Age (years)	84 (80–87)	84 (78–86)	85 (81–87)	0.74
Male sex	21 (37.5)	5 (31)	16 (40)	0.20
BMI (kg/m^2)	22.5 (18.8–24.9)	22.3 (19.0–25.0)	22.7 (18.1–24.8)	0.34
Systolic BP (mmHg)	114 (104–130)	112 (104–130)	110 (102–130)	0.93
Diastolic BP (mmHg)	60 (52–64)	56 (50.5–63)	60 (58–70)	0.13
NYHA III or IV	56 (100)	16 (100)	40 (100)	-
Current smoker	5 (8.9)	2 (12.5)	3 (7.5)	0.18
Presence of hypertension	44 (71.4)	13 (81.3)	31 (77.5)	0.84
Presence of dyslipidemia	23 (4.6)	9 (56.3)	19 (47.5)	0.41
Presence of diabetes	15 (26.7)	5 (31.3)	10 (25)	0.54
Presence of coronary artery disease	15 (26.7)	4 (25)	11 (27.5)	0.95
Prior PCI	11 (19.6)	4 (25)	7 (17.5)	0.45
Prior CABG	5 (8.9)	1 (6.3)	4 (10)	0.70
Prior myocardial infarction	12 (21.4)	4 (25)	8 (20)	0.59
Presence of peripheral artery disease	5 (8.9)	2 (12.5)	3 (7.5)	0.50
Presence of atrial fibrillation	23 (41)	7 (43.4)	16 (40)	0.66
Presence of chronic kidney disease	31 (55.4)	4 (25)	27 (67.5)	0.007
ACEI/ARB use	27 (48.2)	4 (25)	23 (57.5)	0.11
β-Blocker use	17 (30.4)	6 (37.5)	11 (27.5)	0.18
Dose of tolvaptan in a day 3.75/7.5 mg	36/20 (64.3/35.7)	9/7 (56.3/43.8)	27/13 (67.5/32.5)	0.43
Equivalent dose of furosemide in a day, mg	20 (10–20)	20 (20–20)	20 (10–20)	0.36
Aldosterone antagonists use	12	5 (31.2)	7 (17.5)	0.32
Human atrial natriuretic peptide use	1	0 (0)	1 (0.02)	0.52
Echocardiographic parameters				
LVEF (%)	56 (44–63)	50 (42–60)	57 (44–63)	0.20
V_{max} (m/s)	4.0 (3.4–4.7)	3.9 (3.0–5.0)	4.0 (3.4–4.7)	0.84
Mean PG (mmHg)	39 (26–52)	35 (23–55)	40 (27–52)	0.69
SVi (mL/m^2)	41 (34–47)	32 (22–34)	44 (38–50)	< 0.001
Laboratory data				
Creatinine level (mg/dL)	0.99 (0.78–1.45)	0.94 (0.75–1.6)	0.96 (0.86–1.44)	0.07
eGFR (mL/min/1.73 m^2)	44 (30.5–59.9)	44.0 (30.1–62.0)	41.5 (27.6–59.9)	0.06
BUN level (mg/dL)	22.2 (15.8–32.5)	22.7 (17.0–31.4)	21.2 (17.1–36.0)	0.05
Sodium level (mEq/L)	141 (138–144)	140 (138–143)	138 (124–142)	0.90
Potassium level (mEq/L)	4.3 (4.0–4.6)	4.4 (4.1–4.6)	4.3 (3.9–5.2)	0.73
NT-proBNP level (pg/mL)	6639 (2839–18,204)	5731 (2365–16,731)	17 644 (4903–33,583)	0.43

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *BP* blood pressure, *BUN* blood urea nitrogen, *CABG* coronary artery bypass, *eGFR* estimated glomerular filtration rate, *LF* low-flow, *LVEF* left ventricular ejection fraction, *NF* normal-flow, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention, *PG* pressure gradient, *SVi* stroke volume index, V_{max} the maximal velocity of aortic valve

difference in the daily dose of tolvaptan and furosemide ($p = 0.43$ and $p = 0.36$, respectively), and other diuretics used such as oral aldosterone antagonists or intravenous human atrial natriuretic peptide ($p = 0.32$ and $p = 0.52$, respectively) between the two groups (Table 1).

Primary endpoints

No clinical adverse events such as death, worsening heart failure, worsening renal failure, fatal arrhythmia, cardiogenic or hypovolemic shock vital, and use of inotropic agents occurred during the 48 h after the initiation of tolvaptan treatment in the NF-SAS and LF-SAS groups. Tolvaptan therapy yielded significantly higher 24-h and 48-h urine outputs than those at baseline in both groups (NF-SAS group, medians at baseline, 24 h, and 48 h: 1096, 1560, and 1576 mL, respectively, baseline vs. 24-h: $p < 0.01$, baseline vs. 48-h: $p < 0.01$; LF-SAS group, medians: 754, 1623, and 2103 mL, respectively, baseline vs. 24-h: $p < 0.01$, baseline vs. 48-h: $p < 0.01$). There was no significant difference in the increased urine volume between the two groups at 24 and 48 h after tolvaptan administration ($p = 0.23$ and $p = 0.11$, respectively) (Fig. 2a). Meanwhile, tolvaptan treatment resulted in a significant decrease in the total fluid balance at 24 and 48 h after tolvaptan administration compared to baseline in the LF-SAS group (medians at baseline, 24-h, and 48-h: + 164, -31.5, and + 77 mL, respectively, baseline vs. 24-h: $p < 0.05$, baseline vs. 48-h: $p < 0.05$). Although it was not significant, there was a tendency towards a decreased fluid balance in the NF-SAS group at 24 and 48 h after tolvaptan administration (medians at baseline, 24 h, and 4 h: − 25, − 434, and − 446 mL, respectively, baseline vs. 24-h: $p = 0.07$, baseline vs. 48-h: $p = 0.09$). There was no significant difference in the fluid balance between the two groups at 24 and 48 h after tolvaptan administration ($p = 0.36$ and $p = 0.25$, respectively) (Fig. 2b).

Clinical changes before and after tolvaptan treatment

Systolic and diastolic blood pressures did not significantly change in the NF-SAS and LF-SAS groups at 48 h (Fig. 3a, b). Figure 4a–g shows the laboratory findings. The serum sodium level at 48 h significantly increased in both groups [LF-SAS group, baseline median: 138 (IQR 134–142) mEq/L and median at 48 h: 142 (IQR 139–144) mEq/L; NF-SAS group, baseline median: 140 (IQR 138–143) mEq/L and median at 48-h: 143 (IQR 140–144) mEq/L; $p = 0.02$ and $p < 0.01$, respectively]. The serum BUN level at 48 h significantly decreased in the LF-SAS group [baseline median: 21.2 (IQR 17.1–36.0) mEq/L, median at 48 h: 17.9 (IQR 13.9–36.2) mEq/L; $p = 0.045$]. Other laboratory data such as the serum potassium, creatinine, and albumin levels; eGFR; and hematocrit did not change significantly.

Discussion

This study demonstrated several main findings. First, tolvaptan therapy did not show any adverse clinical events in the LF-SAS and NF-SAS groups. Second, adding tolvaptan to furosemide increased the total urinary output and decreased the fluid balance without worsening heart failure in patients with LF-SAS and NF-SAS, which is in line with the results of a previous study [2]. Third, tolvaptan did not affect blood pressure during the acute phase. Regarding laboratory data, the serum sodium level 48 h after tolvaptan administration significantly increased in both groups, and did not require

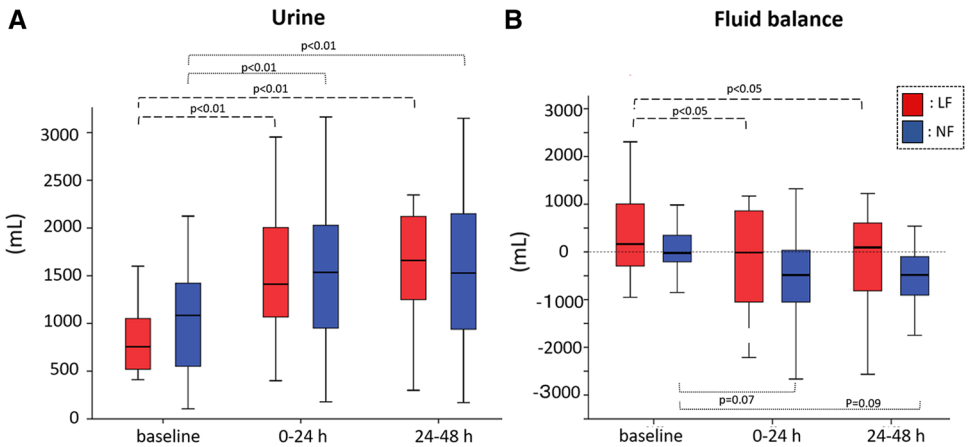

Fig. 2 Urine volume (**a**) and total fluid balance (**b**) from baseline to 48 h after treatment with tolvaptan. Tolvaptan treatment yielded significantly higher urine outputs at 24 and 48 h after tolvaptan administration compared to baseline in the NF-SAS and LF-SAS groups. In addition, tolvaptan treatment significantly decreased the fluid balance at 24 and 48 h after tolvaptan administration compared to baseline in the NF-SAS group. *h* hour, *LF* low-flow, *NF* normal-flow, *SAS* severe aortic stenosis

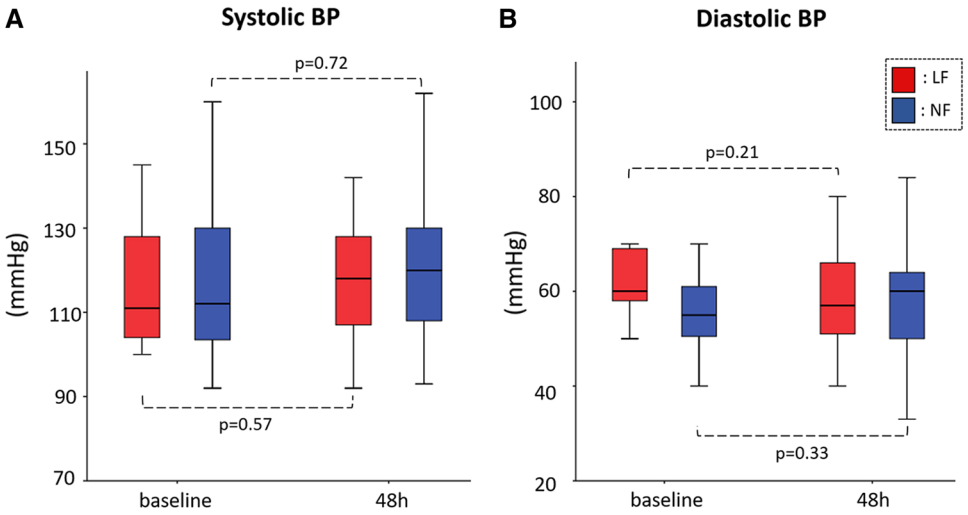

Fig. 3 Changes in blood pressure (**a**, systole; **b**, diastole) at baseline and 48 h after tolvaptan treatment. Systolic and diastolic blood pressures during the 48-h observation period were stable with no significant changes in the NF-SAS and LF-SAS groups. *BP* blood pressure, *LF* low-flow, *h* hour, low-flow, *NF* normal-flow, *SAS* severe aortic stenosis

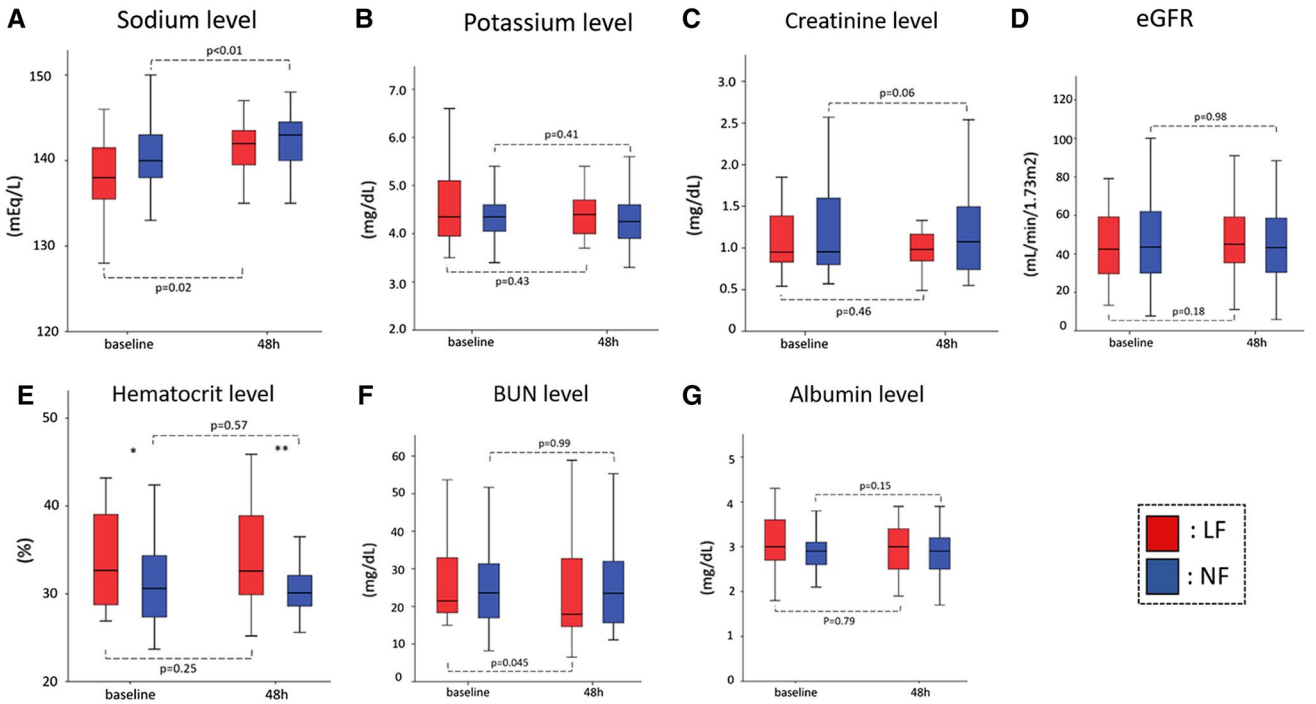

Fig. 4 Changes in the laboratory parameters (**a**, sodium level; **b**, potassium level; **c**, serum creatinine level; **d**, eGFR; **e**, hematocrit level; **f**, BUN level; **g**, albumin level) at baseline and 48 h after tolvaptan treatment. Among all parameters, only the serum sodium level significantly increased after 48 h in the LF-SAS and NF-SAS groups (**a**). $*p<0.01$ between the LF-SAS and NF-SAS groups. $**p<0.05$ between the LF-SAS and NF-SAS groups. *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *h* hour, *LF* low-flow, *NF* normal-flow, *SAS* severe aortic stenosis

any clinical intervention. Therefore, our findings verify our hypothesis that tolvaptan would be a suitable therapy for heart failure with LF-SAS and NF-SAS. To our knowledge, this is the first report to describe the clinical safety and effectiveness of tolvaptan in patients with LF-SAS, and our findings may ease the concerns of clinicians in Japan.

LF-SAS may be attributed to poor contractile left ventricular (LV) function. Patients with LF-SAS typically have slightly lower ejection fractions (EFs) than do patients with NF-SAS [3]. Although not significant, this result was shown in our study. LF status has also been attributed to several pathologies such as a higher global LV afterload, restrictive physiology with pronounced LV concentric hypertrophy, reduced LV compliance and filling, and large subendocardial fibrosis resulting in reduced longitudinal deformation [16–18]. Therefore, LF-SAS is

considered a more advanced stage according to the ACC/AHA guidelines [12]. Among individuals with impaired LV function and hemodynamic instability, patients with LF-SAS are more susceptible to intravascular hypovolemia after using diuretics, which leads to low blood pressure. However, in the present study, tolvaptan did not have an adverse effect on blood pressure, did not cause signs of shock, and did not precipitate the need for any inotropic agents in the LF-SAS and NF-SAS groups. Tolvaptan does not cause intravascular dehydration [8] because it is a vasopressin-2 antagonist, which produces free-water urine and increases serum osmolality, leading to the movement of fluid from the extravascular space to the intravascular space without hemodynamic instability [19, 20]. Our result that the hematocrit and serum albumin levels did not increase 48 h after tolvaptan administration supports this fact.

Our study population was of advanced aged (median age 84 years), and the pathogenesis of AS is due to age-related changes [21]. Kinugawa et al. reported that tolvaptan is effective and safe for use in patients older than 80 years. However, a lower starting dose of tolvaptan, ≤ 7.5 mg, should be considered to prevent hypernatremia [22]. We used a lower dose of tolvaptan (3.75 mg/day in 64.3% of patients and 7.5 mg/day in 35.7%) and observed a similar result. Although significant serum sodium levels were shown 48 h after tolvaptan administration in the LF-SAS and NF-SAS groups, the patients did not require any clinical intervention or discontinuance of tolvaptan therapy. In addition, a lower dose of tolvaptan did not cause hemodynamic instability in patients with LF-SAS who had an increased urinary volume. Therefore, the dose of tolvaptan for elderly patients with LF-SAS should be low. As this was a retrospective study, the clinical safety and effectiveness of high-dose tolvaptan therapy for LF-SAS remains unknown; therefore, a prospective, randomized controlled trial is needed to investigate this further.

In patients with ADHF, worsening renal failure is an indication of poor prognosis [23]. In our study, no worsening of the serum creatinine level, eGFR, and serum BUN level was observed. Therefore, tolvaptan therapy did not cause worsening renal failure in patients with LF-SAS. This finding is consistent with that of previous reports in which tolvaptan did not decrease renal function in patients with ADHF [24, 25]. BUN, which can be used to estimate neurohormonal activation, might predict potential adverse effects of loop diuretics in patients with chronic heart failure [26]. An increase in the BUN level at discharge is associated with mortality in patients with ADHF according to the result of the ATTEND registry [27]. We found that the BUN level significantly decreased in the LF-SAS group, which indicates that tolvaptan may be more favorable than diuretics as it does not affect neurohormonal activation in patients with an LF status in comparison to conventional furosemide. This may be another aspect to consider regarding the efficacy of tolvaptan.

Study limitations

This study has several limitations. First, this was a retrospective single-center study with a small sample size. Second, data on the change in symptoms, respiratory rate, weight, edema, jugular venous dilation, and inferior vena cava diameter or estimate right ventricular systolic pressure by echocardiography, which reflect congestion state or intravascular volume, were lacking. Third, we did not evaluate a non-tolvaptan group as a control group, which would be better to compare the efficacy of tolvaptan. Fourth, the observation period was short and included only the acute phase (up to 48 h after tolvaptan administration). Fifth, LF-SAS is generally divided into two subtypes: classic LF-SAS, which is defined by an aortic valve area ≤ 1.0 cm^2 and LVEF < 50%, and paradoxical LF-SAS, which is defined by an aortic valve area ≤ 1.0 cm^2, LVEF ≥ 50%, and stroke volume index < 35 mL/m^2. In this study, the patients were not divided by those subtypes because of the small sample size. In addition, a low-gradient status, which is usually considered as another subtype of SAS, was not considered [12]. Therefore, a larger population from a multi-center study with a longer follow-up period is required to compensate for these limitations and strengthen the evidence of the safety and effectiveness of tolvaptan. We are currently conducting a multicenter prospective study, LOw-Dose Tolvaptan in Decompensated Heart Failure Patients with Severe Aortic Stenosis (LOHAS registry), and the results will be published in the near future.

Conclusions

Adding tolvaptan to furosemide increased the urine output and decreased the fluid balance more than that of conventional furosemide treatment, without renal dysfunction and hypotension in patients with SAS including those with LF, who did at least as well. Our results provide evidence of the safety and efficacy of tolvaptan in light of the ongoing debate concerning diuretic treatment in patients with SAS and ADHF. Further prospective studies are needed to clarify the clinicians' concern regarding diuretic treatment in patients with SAS.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval The ethics committee of our institution approved the study protocol (number TEIRIN 17-111). The study protocols were developed in accordance with the ethical guidelines of the Declaration of Helsinki. This observational trial was registered with the University Hospital Medical Information Network (number UMIN R000036168).

Informed consent The need for informed consent was waived because of the retrospective study design.

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