Effectiveness and Safety of Tolvaptan in Patients with Aortic Stenosis

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Summary: Background: Heart failure in severe aortic stenosis (AS) before aortic valve has a poor prognosis with high risk. Although the overuse of loop diuretics may induce hypovolemia, cardiac output reduction, and critical hypotension in severe AS, tolvaptan is characterized by its ability to help maintain hemodynamics and seems to be appropriate for use in heart failure caused by AS. Therefore, we retrospectively examined the effects and safety of tolvaptan use in patients with heart failure caused by severe AS.

Methods and Results: Ten patients with heart failure caused by severe AS were enrolled. Tolvaptan administration did not cause blood pressure decrease significantly, whereas urine volume increased significantly from 896±318 to 1322±502 mL/day (P<0.05). Although there was no statistical significance, functional classes tended to be improved. Blood tests indicated no worsening of kidney function and N-terminal pro-brain natriuretic peptide levels after the use of tolvaptan. Echocardiography also showed no hypovolemia and no worsening of aortic valve flow (18.3±3.8 to 15.5±5.5 cm/s, n.s).

Conclusions: Tolvaptan use in AS patients with heart failure is effective and safe before aortic valve intervention.

Keywords heart failure, aortic stenosis, tolvaptan, aortic valve velocity, intravascular volume, blood pressure, urine volume

INTRODUCTION

Aortic stenosis (AS) is one of the major valvular heart diseases in an aging society [1,2]. In terms of its natural history, AS patients may remain asymptomatic for a long period [3]; however, after patients with AS suffer from symptoms, the prognosis is poor in severe AS, with a reported survival rate of only 15-50% at 5 years [3]. Sudden cardiac death often occurs in symptomatic patients, but is rare in truly asymptomatic patients with severe AS (<1% per year) [3].

The main symptoms in patients with severe AS are exertional dyspnea, angina, syncope, and ultimately heart failure [4]. It is reported that the average survival is 2 years after heart failure occurs [4]. Initially, heart failure symptoms occur during preserved left ventricular ejection fraction [5]. Although diuretics are usually used before surgical treatment to improve congestion [5], the overuse of loop diuretics may induce hypovolemia, cardiac output reduction, and critical hypotension in severe AS.

Tolvaptan is one of the vasopressin type 2 receptor antagonists, which are novel diuretics to treat congestive heart failure [6]. Tolvaptan is characterized by the improvement of congestive symptoms, hyponatremia, and relatively well-maintained hemodynamics [6]. Due to the differences of clinical features between tolvaptan and loop diuretics [7], tolvaptan seems to be better for treating heart failure caused by AS, so far as hemodynamics and renal function are concerned [8]. Therefore, we retrospectively examined the effects and safety of tolvaptan use in patients with heart fail-
ure caused by severe AS.

METHODS

This study complies with the Declaration of Helsinki, and the Ethics Committee of Kurume University Hospital approved the study protocol. The authors had full access to the data and take full responsibility for its integrity.

Study population

All patients with heart failure caused by severe AS, who required additional diuretics to treat heart failure after hospitalization, from April 2015 to March 2019, were enrolled in the present study. All patients with heart failure were diagnosed according to the Framingham criteria [9].

Data Collections

Baseline demographic data were collected based on medical records, including age, sex, height, body weight, waist, medications, risk factors (hypertension, glucose intolerance/diabetes mellitus and dyslipidemia), blood pressure, pulse rate, heart rate, and comorbidities (coronary artery disease, hypertensive heart disease, cardiomyopathy, valvular heart diseases, and congenital heart diseases) [10].

Blood sampling

After overnight fast, peripheral blood was drawn from the antecubital vein for measurements of blood cell counts, lipid profiles, liver and renal function markers, glycemic parameters, uric acid, and N-terminal pro-brain natriuretic peptide (NT-proBNP) [10]. These chemistries were measured at a commercially available laboratory in Kurume University Hospital [10].

Electrocardiography

A 12-lead electrocardiography (ECG, 10 mm = 1 mV, 25 mm/s) was acquired in a supine position during quiet respiration (ECG-1550; NIHON KOHDEN, Fukuoka, Japan) [10]. ECG findings including rhythm were assessed.

Echocardiography

Echocardiograms were obtained using a commercially available ultrasound unit, General Electric Vivid 9 (GE Healthcare, Horten, Norway), and stored on a dedicated workstation for off-line analysis (EchoPAC, GE Healthcare) by well-trained sonographers [10]. All echocardiographic parameters were calculated according to the American Society of Echocardiography guidelines [10]. All data, including demographic data, blood tests, and echocardiography, were obtained before and 10 to 14 days after tolvaptan administration.

Statistical analysis

Data were presented as mean ± standard deviation. The Shapiro-Wilk test was performed to evaluate the assumption of normality. Statistical analysis was performed by means of appropriate parametric and nonparametric methods. Unpaired Student t test was performed for comparisons between pre- and post-tolvaptan therapy. Chi-square test was used for categorical variables. Values of p < 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of the JMP® 14 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients Characteristics

Ten patients with heart failure caused by severe AS (2 males and 8 females, age 83.1 ± 4.4 years old) were enrolled in the present study. There were 4 patients with atrial fibrillation, 2 ischemic heart disease, 6 hypertension, 5 diabetes mellitus, and 4 dyslipidemia (Table 1). The mean dosage of loop diuretics was 38 mg/day as calculated by furosemide, and 12.5 mg/day of spironolactone (Table 2).

Efficacy and Safety of Tolvaptan

In all 10 patients, no tolvaptan was administered at baseline (Table 2). After we administered tolvaptan, blood pressure did not significantly decrease and urine volume was significantly increased (Table 2). There were no statistically significant differences in furosemide dose before and after tolvaptan (Table 2), however functional classes and clinical assessment tended to be improved (Figure 1 and Table 3). Blood tests indicated no worsening of kidney function and NT-proBNP levels after the use of tolvaptan (Table 2). Echocardiography also showed no hypovolemia and no worsening of aortic valve flow (Table 4). In chronic phases, 8 out of 10 patients received aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). The other 2 patients were discharged from our hospital without aortic valve intervention due to social reasons.

DISCUSSION

The novel finding of the present study was that
Tolvaptan increased urine volume and improved heart failure symptoms without significant change of aortic valve flow in patients with severe AS. In patients with severe AS, reduced blood volume caused by diuretics can increase aortic valve flow and worsen AS severity. Tolvaptan has a diuretic effect without causing hemodynamic changes in severe AS, probably due to preserved intravascular volume, which is a clinically important issue. In patients with pulmonary congestion in severe AS, surgical treatment is indicated after diuretics reduce congestion; however, loop diuretics may decrease intravascular volume and increase aortic valve flow, leading to worsening of the AS. In contrast, tolvaptan is a useful tool because it is able to reduce congestion without decreasing intravascular volume in severe AS.

Exertional dyspnea, one of the most common features in patients with AS, may be caused by impaired left ventricular diastolic function, in which end-diastolic pressure excessively rises, leads to pulmonary congestion, and limits the ability to increase cardiac output with exercise [3,5]. It is known that more severe exertional dyspnea, including orthopnea or pulmonary edema, are associated with increased pulmonary venous pressure [3]. In current practice, surgical or transcatheter intervention is typically undertaken before this disease stage [3].

To increase the safety of surgical or transcatheter intervention, patients with heart failure and volume overload should be prepared before the procedure [3]. Diuretics are usually used to reduce congestion prior to valve intervention. Otherwise, nitroprusside or

![Fig. 1. Heart failure status before and after tolvaptan.](image)

**TABLE 1.**

| Patient | Pt 1 | Pt 2 | Pt 3 | Pt 4 | Pt 5 | Pt 6 | Pt 7 | Pt 8 | Pt 9 | Pt 10 |
|---------|------|------|------|------|------|------|------|------|------|-------|
| Sex     | F    | F    | F    | F    | F    | M    | F    | M    | F    | F/M 8/2 |
| Age     | 87   | 81   | 83   | 80   | 85   | 90   | 83   | 86   | 83   | 83.1±4.4 |
| AF      | N    | Y    | N    | N    | Y    | N    | Y    | N    | N    | Y/N 4/6 |
| CAD     | N    | N    | Y    | N    | Y    | N    | N    | N    | N    | Y/N 2/8 |
| HT      | Y    | Y    | Y    | N    | N    | Y    | N    | Y    | Y    | Y/N 6/4 |
| DM      | Y    | N    | Y    | Y    | N    | Y    | N    | N    | N    | Y/N 5/5 |
| DyL     | N    | N    | Y    | Y    | N    | Y    | N    | N    | N    | Y/N 4/6 |

AF=atrial fibrillation, CAD=coronary artery disease, HT=hypertension, DM=diabetes mellitus, DyL=dyslipidemia, F=female, M=male, N=no, Y=yes
| TABLE 2. | Clinical characteristics before and after tolvaptan |
|----------|-----------------------------------------------|
| Tolvaptan | Pt 1 | Pt 2 | Pt 3 | Pt 4 | Pt 5 | Pt 6 | Pt 7 | Pt 8 | Pt 9 | Pt 10 | mean | P value |
| NYHA pre | III | II | II | III | II | II | III | II | III | II | 121.2 | 0.1213 |
| post | II | I | II | II | II | II | II | II | II | II | 111.0 | |
| Nohria-Stevenson pre | L | B | B | C | B | B | B | B | B | B | 84.8 | 0.0988 |
| post | L | B | B | C | A | A | B | B | B | A | 45.4 | 0.487 |
| Systolic BP (mmHg) pre | 138 | 131 | 129 | 85 | 112 | 125 | 125 | 104 | 133 | 130 | 121.2 | 0.1213 |
| post | 97 | 110 | 122 | 94 | 116 | 131 | 119 | 88 | 102 | 122 | 111.0 | |
| Diastolic BP (mmHg) pre | 98 | 85 | 61 | 58 | 74 | 83 | 54 | 70 | 75 | 90 | 74.8 | 0.0988 |
| post | 49 | 77 | 58 | 51 | 74 | 75 | 56 | 58 | 71 | 78 | 64.7 | |
| Pulse pressure (mmHg) pre | 40 | 46 | 68 | 27 | 38 | 42 | 71 | 34 | 58 | 40 | 46.4 | 0.8707 |
| post | 48 | 33 | 64 | 43 | 42 | 56 | 63 | 30 | 31 | 44 | 45.4 | 0.487 |
| Heart rate (bpm) pre | 75 | 81 | 85 | 68 | 103 | 75 | 55 | 96 | 89 | 120 | 84.7 | 0.4087 |
| post | 70 | 81 | 71 | 80 | 88 | 75 | 58 | 90 | 63 | 108 | 78.4 | |
| Body weight (kg) pre | 54.7 | 54 | 51.1 | 35 | 38.2 | 54.4 | 31.3 | 54 | 51.7 | 56.9 | 48.2 | 0.9204 |
| post | 54.3 | 51.8 | 50.5 | 35.8 | 36.2 | 55.1 | 32.7 | 53 | 51.8 | 56.2 | 47.7 | 0.0361 |
| Urine volume (mL) pre | 800 | 1080 | 900 | 750 | 960 | 350 | 450 | 1100 | 1320 | 1250 | 896 | 0.0361 |
| post | 1020 | 1990 | 1200 | 2160 | 1220 | 1380 | 450 | 910 | 1590 | 1300 | 1322 | |
| Medication | | | | | | | | | | | | |
| Furosemide pre | 60 | 40 | 20 | 60 | 40 | 20 | 40 | 20 | 38.0 | 0.7075 |
| post | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36.0 | 0.7915 |
| Azosemide pre | 0 | 0 | 0 | 0 | 60 | 0 | 60 | 0 | 0 | 0 | 0 | 0.2643 |
| (mg) post | 0 | 0 | 0 | 0 | 60 | 0 | 60 | 0 | 0 | 0 | 0 | 0.2643 |
| Furosemide equivalent dose pre | 60 | 40 | 20 | 60 | 40 | 20 | 40 | 40 | 40 | 20 | 38.0 | 0.7915 |
| (mg) post | 0 | 0 | 0 | 0 | 60 | 0 | 60 | 0 | 0 | 0 | 0 | 0.2643 |
| Spironolactone pre | 0 | 25 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 12.5 | 0.2643 |
| (mg) post | 0 | 25 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 20.0 | 0.2643 |
| Dobutamine pre | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.2643 |
| (µg/kg/min) post | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.2643 |
| Tolvaptan initial dose | 7.5 | 15 | 3.75 | 7.5 | 15 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 6.75 | 0.2643 |
| (mg) post | 15 | 15 | 15 | 7.5 | 15 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 10.88 | 0.2643 |
| Blood test | | | | | | | | | | | | |
| BUN pre | 42.3 | 21.1 | 53.9 | 40.2 | 21.9 | 17.1 | 26.8 | 18.4 | 14.9 | 46.2 | 30.3 | 0.4312 |
| (mg/dL) post | 54.6 | 29.4 | 38.5 | 60.1 | 22.6 | 20.5 | 39.6 | 26.1 | 23.2 | 38 | 35.3 | |
| Creatinine pre | 1.5 | 0.79 | 2.42 | 1.19 | 0.84 | 0.77 | 1.59 | 1.19 | 0.71 | 1.65 | 1.27 | 0.9607 |
| (mg/dL) post | 1.74 | 1.06 | 1.63 | 1.17 | 0.78 | 0.82 | 1.42 | 1.42 | 1.03 | 1.48 | 1.26 | 0.9607 |
| eGFR (mL/min/1.73 m²) pre | 25.5 | 52.6 | 15.3 | 33.7 | 48.5 | 71 | 24.3 | 44.7 | 58.7 | 24.2 | 39.9 | 0.6688 |
| post | 21.7 | 38.1 | 23.6 | 34.3 | 52.6 | 66.3 | 27.5 | 36.8 | 39.1 | 27.3 | 36.7 | 0.6688 |
| Na pre | 139 | 145 | 131 | 135 | 142 | 145 | 141 | 140 | 141 | 143 | 140.2 | 0.6508 |
| (mEq/L) post | 140 | 137 | 140 | 136 | 138 | 143 | 141 | 140 | 140 | 140 | 139.5 | 0.6508 |
| K pre | 4.5 | 3.1 | 4.9 | 4.4 | 3.4 | 3.5 | 3.7 | 3.5 | 4.5 | 5.6 | 4.1 | 0.4960 |
| (mEq/L) post | 4.2 | 4.3 | 4.7 | 4.4 | 4.3 | 3.9 | 4.3 | 4.3 | 4.3 | 4.9 | 4.3 | 0.4960 |
| NT-proBNP pre | 9791 | 5956 | 7822 | 12024 | 3881 | 3824 | 32101 | 1865 | 257 | 14530 | 9205 | 0.7393 |
| (pg/mL) post | 6823 | 4498 | 7667 | 4850 | 2242 | 3290 | 23063 | 2887 | 228 | 11350 | 11059 | 0.7393 |

NYHA=New York Heart Association, A=warm & dry, B=warm & wet, L=cold & dry, C=cold & wet, BP=blood pressure, BUN=blood urea nitrogen, Crea=creatinin, eGFR=estimated glomerular filtration rate, NT-proBNP= N-terminal pro-brain natriuretic peptide.
### TABLE 3.
Functional class and clinical profiles before and after tolvaptan

| NYHA  | I   | II  | III | IV  |
|-------|-----|-----|-----|-----|
| Tolvaptan | pre | 0   | 5   | 5   | 0   |
|        | post| 1   | 9   | 0   | 0   |
| Nohria-Stevenson | A   | B   | L   | C   |

Tolvaptan | pre | 0   | 8   | 1   | 1   |
|          | post| 3   | 5   | 1   | 1   |

NYHA=New York Heart Association, A=warm & dry, B=warm & wet, L=cold & dry, C=cold & wet.

### TABLE 4.
Echocardiographic characteristics before and after tolvaptan

| Tolvaptan | Pt 1 (mm) | Pt 2 (mm) | Pt 3 (mm) | Pt 4 (mm) | Pt 5 (mm) | Pt 6 (mm) | Pt 7 (mm) | Pt 8 (mm) | Pt 9 (mm) | Pt 10 (mm) | mean | P value |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|---------|
| LVDDd     | 41.1      | 34.8      | 50        | 48.9      | 56        | 51        | 50        | 63        | 33        | 45.5      | 47.3  | 0.7075  |
| LVDs      | 20.7      | 21.9      | 36        | 40.8      | 46        | 34        | 30        | 53        | 20        | 40        | 34.2  | 0.9641  |
| LA        | 41.1      | 54.5      | 38        | 50.7      | 46        | 45        | 50        | 41        | 35        | 50.9      | 45.2  | 0.2807  |
| IVS       | 14.1      | 18.8      | 7         | 11.4      | 6         | 12        | 9         | 7         | 11        | 9.1      | 10.5  | 0.392   |
| PWT       | 13.9      | 17.8      | 8         | 10.7      | 9         | 12        | 8         | 8         | 10        | 10       | 10.7  | 0.5329  |
| LV EF (%) | 81.2      | 68.1      | 50        | 34.5      | 45        | 57.3      | 70.3      | 33        | 70        | 30.2     | 54.0  | 0.5508  |
| IVC       | 12.2      | 22.7      | 17        | 14.5      | 24        | 16.5      | 17        | 20        | 17.4      | 22.1     | 18.3  | 0.195   |
| AV peak velocity (cm/s) | 6         | 19        | 15        | 8         | 13.1      | 17        | 24        | 14.5      | 17.1      | 21.2     | 15.5  |         |
| Mean systolic PG(AoV) (mmHg) | 113.5     | 62        | 15        | 55        | 15        | 58.1      | 28.9      | 45        | 17.5      | 16       | 42.6  | 0.8172  |
| AVA (cm²) | 0.45      | 0.31      | 0.57      | 0.22      | 0.69      | 0.65      | 0.62      | 0.66      | 0.79      | 1        | 0.60  | 0.8324  |
| RA-RV-ΔPG (mmHg) | 51        | 81        | 43        | 0         | 35        | 36        | 77        | 52        | 33        | 49       | 45.7  |         |
| E/e'      | 37.9      | 31.1      | 38.3      | 50        | 11.2      | 29.3      | 24.1      | 27.3      | 16        | 15.6     | 28.1  | 0.9093  |

AoV=aortic valve, AVA=aortic valve area, IVC= inferior vena cava, IVS=interventricular septum, LA=Left atrium, LVDD=Left ventricular dimension (end-diastolic), LVDs=Left ventricular dimension (systolic), LVEF=left ventricular ejection fraction, MR=mitral valve regurgitation, PG=pressure gradient, PWT=posterior LV wall thickness, RA=right atrium, RV=right ventricle, TR=tricuspid valve regurgitation.
phosphodiesterase type 5 inhibitor has been shown to provide improvements in pulmonary and systemic hemodynamics to unload the left heart, reduce congestion, and improve forward flow [11,12]. These medications may improve the patients’ hemodynamic status, allowing the interventional procedure to be performed more easily.

Study Limitations
Several limitations of the present study should be mentioned. First, this was a single center, retrospective study with a small number of patients. Second, the prognostic impact of tolvaptan in AS patients remains to be examined in future studies, keeping in mind that such patients need aortic valve intervention. However, tolvaptan use in AS patients with heart failure may improve hemodynamics before AVR or TAVI, which may lead to safer intervention for AS. Third, we have no data regarding free water clearance and fractional excretion of sodium.

CONCLUSIONS
In conclusion, our study demonstrates that tolvaptan use in AS patients with heart failure is effective and safe before aortic valve intervention.

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