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Right ventricular enlargement predicts responsiveness to tolvaptan in congestive heart failure patients with reduced ejection fraction

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ABSTRACT

Background: Tolvaptan is a vasopressin type 2 receptor antagonist used in heart failure (HF) with refractory diuretic resistance. However, since tolvaptan is also ineffective in some HF patients with reduced ejection fraction (HFrEF), the identification of responders is important.

Methods: The study population consisted of 51 HFrEF patients who were administered tolvaptan (EF, 28 ± 7%). We defined responders as patients with a ≥50% increase in urine volume during the 24-hours after administration of tolvaptan. All patients underwent comprehensive transthoracic echocardiography before administration of tolvaptan. Patients were followed for 120 days to ascertain secondary events (cardiac death and rehospitalization for HF).

Results: Multiple regression analysis indicated that right ventricular (RV) enlargement (defined as basal RV diameter > 41 mm and midlevel RV diameter > 35 mm, according to guidelines) remained a predictor of response after adjustment for age, sex, starting dosage of tolvaptan, and estimated glomerular filtration rate (odds ratio, 4.88; 95%-confidence interval, 1.26–18.9; $P < 0.05$), whereas left ventricular parameters and RV dysfunction were not. Kaplan-Meier curves indicated responsiveness to tolvaptan was associated with better prognosis among the overall population ($P < 0.05$); similar trends were observed among patients with RV dilatation ($P = 0.056$).

Conclusions: These findings suggest that RV enlargement, which represents right-sided volume overload, elevated filling pressure, and diastolic dysfunction similar to that seen in constrictive pericarditis, predicts responsiveness to tolvaptan in patients with HFrEF. Moreover, administration of tolvaptan may have the potential to improve the reportedly poor prognosis for HFrEF patients with RV dilatation.

1. Introduction

Tolvaptan, an oral, selective vasopressin type 2 receptor antagonist, has become available for decompensated heart failure (HF) patients with refractory diuretic resistance, especially those with severe hyponatremia [1–5]. Tolvaptan therapy enables early improvement of dyspnea and increased urine volume without affecting blood electrolyte levels, activation of the renin-angiotensin-aldosterone system or the sympathetic nerve system, or worsening renal function [6–11]. However, because tolvaptan is also ineffective in some HF patients with a reduced ejection fraction (HFrEF), the identification of responders is important. Although a decrease in urine osmolality after administration was associated with responsiveness to tolvaptan [12], we cannot predict responsiveness before administration using this method. Similarly, it is difficult to measure urine aquaporin-2, a reported novel predictor of response to tolvaptan, because of its cost [13,14].

An alternative method is transthoracic echocardiography (TTE). TTE plays an essential role in HF treatment because of its incomparable ability to provide noninvasive, repeatable, and less expensive assessment at the bedside. Moreover, TTE provides reliable assessment of right- and left-side hemodynamics, cardiac function, and cardiac structure, equivalent to catheter-based techniques [15–17]. However, the association between TTE parameters and responsiveness to tolvaptan has not been elucidated in HFrEF patients with volume overload.

The aim of the present study was, therefore, to assess the relationship between echocardiographic parameters (cardiac structure, cardiac function, and hemodynamics) and responsiveness to tolvaptan in patients with HFrEF.

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2. Methods

2.1. Study population

This observational study conducted at Osaka City University Hospital was designed to clarify the echocardiographic findings associated with responsiveness to tolvaptan in patients with HFrEF. We defined reduced EF as left ventricular EF (LVEF) < 40%, according to published guidelines [4]. The study population comprised 51 consecutive inpatients with congestive HFrEF who received tolvaptan, with sustained excess body fluid that had not resolved despite receiving either of the following diuretic therapies with no change in dose: a loop diuretic of any dose, or combination therapy with a loop diuretic and an aldosterone antagonist of any dose. Concomitant use of the following drugs with no change in the dose was allowed: human atrial natriuretic peptide, catecholamines, and injected diuretics. The attending physician determined the administration, starting dosage, and duration of tolvaptan use according to each patient's condition. All patients had a New York Heart Association functional class of either III or IV. We excluded patients with any mechanical support, severe valvular stenosis, or a history of acute coronary syndrome within 30 days. Free water consumption was encouraged and daily salt intake was limited to 6 g/day for all patients. Urine output was measured for 24 h before and after administration of tolvaptan. Blood samples and vital signs were taken just before administration of tolvaptan. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Definition of responder

We defined responders as patients with a ≥50% increase in urine volume during the 24 h after administration of tolvaptan [18].

2.3. Transthoracic echocardiography

TTE was performed prior to administration of tolvaptan using an iE33 (Philips Medical Systems, Andover, MA, USA), Aplio500 (Canon Medical Systems Corporation, Tochigi, Japan), or Vivid E9 (GE Healthcare, Milwaukee, WI, USA) machine equipped with a high-frequency transducer. A comprehensive examination was performed according to recommendations from the American society of Echocardiography and the European Association of Cardiovascular Imaging [19]. LVEF was calculated with the modified Simpson's method [19]. Inspiratory and expiratory inferior vena cava (IVC) diameters were measured from a subcostal view. IVC collapsibility index was calculated as [(expiratory IVC diameter – inspiratory IVC diameter)/expiratory IVC diameter] [20]. Right Ventricular (RV) diameter was measured from an RV-focused four-chamber view at the base level (D1) and midlevel (D2). RV dilatation was defined as D1 > 41 mm and D2 > 35 mm according to recommendations (Fig. 1) [19]. RV systolic function was evaluated using RV fractional area change and RV systolic dysfunction was defined as RV fractional area change <35% [19]. Estimated systolic pulmonary artery pressure was derived from RV systolic pressure by measuring the maximum tricuspid regurgitation jet velocity, and right atrial pressure was estimated by measuring the diameter and collapsibility of the IVC [21].

2.4. Clinical outcomes

The study had complete outcome information (cardiac death or rehospitalization for HF) for all patients within 120 days.

2.5. Statistical analysis

Statistical analysis was performed using SPSS statistics version 24 software (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as percentages. The distribution of echocardiographic variables and potential covariates was evaluated in the overall population and among patients with and without responsiveness to tolvaptan. Comparisons between groups were performed by using the unpaired Student's *t*-test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression analysis adjusted for age, sex, estimated glomerular filtration rate (eGFR), and starting dosage of tolvaptan was used to identify the echocardiographic variables associated with responsiveness to tolvaptan. Echocardiographic variables were entered into logistic regression analysis separately. Then, the survival rates were analyzed using Kaplan-Meier curves according to the responsiveness to tolvaptan therapy among the overall population and patients with RV dilatation, and significant differences were calculated using the log-rank test. We used the Kappa statistic to calculate inter and intra observer agreement of RV parameters. A *P* value of <0.05 was considered statistically significant for all tests.

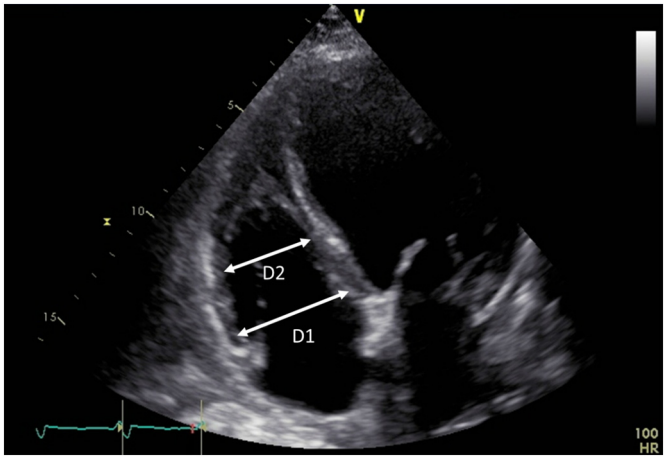

Fig. 1. Echocardiographic assessment of RV dimensions from a, RV-focused apical four-chamber view. D1 = maximum transverse dimension during the basal one-third of RV inflow at end diastole D2 = transverse dimension during the middle third of RV inflow at end diastole. RV, right ventricular.

3. Results

3.1. Patient characteristics

Among the 51 patients (mean age, 70 ± 12 years; LVEF, 28 ± 7%), 24 were responders to tolvaptan (47%). Clinical characteristics according to responsiveness to tolvaptan are shown in Table 1. The study population predominantly consisted of males (75%) with nonischemic cardiomyopathy (57%), chronic kidney disease (eGFR, 45 ± 24 mL/min/1.73 m^2), and moderate furosemide dosage (54 ± 47 mg/day). Female gender ($P = 0.06$) and starting dose of tolvaptan ($P = 0.07$) tended to be associated with responsiveness to tolvaptan, whereas the other patient information was not significantly different between the 2 groups. Although there was no significant difference in urine volume during the 24 h before administration of tolvaptan (1216 ± 324 mL vs. 1464 ± 803 mL, $P = 0.18$) or increased water intake (195 ± 417 mL/day vs. 203 ± 408 mL/day, $P = 0.95$) during the 24 h after administration, urine volume significantly increased during the 24 h after administration in responders (2572 ± 856 mL vs. 1508 ± 814 mL, $P < 0.01$).

3.2. Echocardiographic characteristics

The echocardiographic characteristics according to responsiveness to tolvaptan are shown in Table 2. The study population consisted of patients with severely decreased LVEF (28 ± 7%), dilated LV