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Combination of Urinary Sodium/Creatinine Ratio and Plasma Brain Natriuretic Peptide Level Predicts Successful Tolvaptan Therapy in Patients with Heart Failure and Volume Overload

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Summary

To evaluate short-term clinical and hemodynamic effects of tolvaptan therapy and to identify predictors of the therapeutic outcomes, we retrospectively recruited sixty consecutive hospitalized heart failure (HF) patients (70 ± 11 years) with volume overload. The subjects were divided into two groups on the basis of the changes in HF symptom scores and hemodynamic status assessed by right heart catheterization after tolvaptan therapy (median: 7 days). The majority of patients were successfully treated (Group 1). However, 22% of patients (Group 2) were unsuccessfully treated, in whom 1) HF symptom score worsened or 2) there was a stationary HF symptom score ≥6 points, and mean PCWP >18 mmHg and mean RAP >10 mmHg, after tolvaptan therapy. HF symptom scores, hemodynamic parameters and plasma brain natriuretic peptide (BNP) level improved in Group 1, but all of these parameters remained unchanged in Group 2. Lower urine sodium/creatinine ratio (UNa/UCr) and higher BNP level at baseline were independently associated with unsuccessful tolvaptan therapy, and UNa/UCr best predicts unsuccessful tolvaptan therapy with a cut-off value of 46.5 mEq/g·Cr (AUC 0.858, 95% CI: 0.743-0.974, sensitivity 81%, specificity 77%, p <0.01). Double-positive results of UNa/UCr <46.5 mEq/g·Cr and plasma BNP level >778 pg/ml predicted unsuccessful tolvaptan therapy with high diagnostic accuracy (sensitivity 54%, specificity 100%, positive predictive value 100%, negative predictive value 89% and accuracy 90%). In summary, short-term tolvaptan therapy ameliorated HF symptoms and provided hemodynamic improvement in the majority of patients, and UNa/UCr and BNP level strongly predicted the therapeutic outcomes.

Key Words: vasopressin V2-receptor antagonist; loop diuretics; diuresis; heart failure

Fluid removal is an important component of heart failure (HF) treatment to reduce systemic and pulmonary congestion and relieve signs and symptoms of edema. Recent clinical and experimental studies have demonstrated that selective vasopressin V2 receptor antagonism by oral tolvaptan administration inhibits free water reabsorption in the kidney's collecting tubules, and therefore stabilizes hemodynamic state, ameliorates congestion and edema, and corrects hyponatremia.[1-10] Successful oral tolvaptan therapy can support early ambulation, and can minimize the need for and duration of hospitalization.

An increment in urine volume has been recognized as the best indicator of clinical response to tolvaptan therapy in most studies;[3,6,11,12] however, it has not been fully investigated whether increment of urine volume and resultant body weight loss achieved by V2 receptor antagonism always lead to symptom relief and sufficient hemodynamic improvement.[13] Therefore, we evaluated the effects of oral tolvaptan therapy on short-term clinical course by quantitatively assessing symptoms and hemodynamic states in patients with HF and volume overload. In addition, we identified the predictors of the therapeutic outcomes.

Methods

Subjects: This clinical investigation was approved by the Human Studies Subcommittee of Mie University Graduate School of Medicine (reference number: 2777). The study complies with the Declaration of Helsinki. All patients gave written informed consent. We retrospectively investigated

60 consecutive in-hospital patients with decompensated HF who received oral tolvaptan therapy for the treatment of volume overload between December 2010 and December 2014 in our cardiology ward. The HF symptoms of all patients worsened despite receiving HF treatment including oral diuretic therapy before hospital admission. Daily salt intake was limited to 6 g/day in all patients during hospitalization. Patients who required cardiac intensive care because of "non-ambulatory" New York Heart Association (NYHA) class IV HF including cardiogenic shock were not included in the present study.

Procedure: All patients underwent baseline blood and urine tests including neurohumoral assessment in the early morning before breakfast, chest X-ray, echocardiography and hemodynamic measurements with right heart catheterization. Vital signs, 24-hour fluid intake and urine volume were measured at baseline and every 24 hours thereafter. Body weight was measured after urination and before breakfast at baseline and every subsequent day during tolvaptan therapy. Estimated glomerular flow rate (eGFR) was calculated using an equation modified for the Japanese.[14)] First-morning spot urine tests included the measurements of osmolality, sodium (UNa) and creatinine (UCr). Since we failed to measure urine urea nitrogen (UUN) in about half of patients, the following formula was used to estimate UUN.[15)]

Urine osmolality = $1.07 \times \{2 \times [\text{UNa (mEq/L)}] + [\text{UUN (mg/dl)}] / 2.8 + [\text{UCr (mg/dl)}] \times 2/3\} + 16$.

It was planned that all patients would undergo repeated blood and urine tests, chest X-ray, echocardiography and right heart catheterization 7 days after the initiation of tolvaptan therapy. HF

symptom score was calculated as the summation of scores that were assigned to symptoms due to HF, such as (1) pitting edema in the lower extremities [1 point], (2) pulmonary congestion [1 point], (3) jugular venous distention [1 point], (4) dyspnea [1 point], and (5) degree of NYHA (1-4 points were assigned for each class, e.g. 4 points were assigned for NYHA class IV) before and 7 days after tolvaptan therapy.[3,16)]

Neurohumoral assessment: Plasma B-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels, plasma renin activity, plasma aldosterone concentration and plasma arginine-vasopressin level were obtained after at least 15 minutes of rest in a sitting position, before drug ingestion and before breakfast. Blood samples for the determination of plasma BNP and ANP levels were collected in a tube containing potassium ethylenediaminetetra-acetic acid, kept at room temperature and analyzed within 4 hours of collection. Plasma renin activity, plasma aldosterone concentration and plasma arginine-vasopressin level were measured by a radioimmunoassay at a commercial laboratory (SRL, Tokyo, Japan).[5)]

Echocardiographic assessment: Left ventricular end-diastolic dimension and end-systolic dimension were assessed from the parasternal long-axis view. Left ventricular ejection fraction was assessed using the biplane Simpson's rule.

Hemodynamic assessment: During right heart catheterization, mean pulmonary capillary wedge pressure (PCWP), mean right arterial pressure (RAP), systolic pulmonary artery pressure (PAP), mean PAP, diastolic PAP and estimated cardiac output were recorded.[5)] Arm-cuff blood pressure

measurements were performed simultaneously with right heart catheterization. The following formulas were used to calculate standard hemodynamic parameters derived from the above measurements.

Cardiac index = cardiac output / body surface area

Systemic vascular resistance index = (mean blood pressure – mean RAP) × 80 / cardiac index

Classification of successful and unsuccessful tolvaptan therapy: Patients were divided into two groups according to their clinical course during tolvaptan therapy. They were classified as being successfully treated (Group 1) if they did not meet either of the following two criteria, and they were classified as being unsuccessfully treated (Group 2) if they met at least one of them: 1) HF symptom score worsened or 2) the presence of a stationary HF symptom score ≥6 points, and mean PCWP >18 mmHg and mean RAP >10 mmHg, after tolvaptan therapy.

Statistical analysis: All numerical data are expressed as the mean ± standard deviation or median (interquartile range). Continuous data were compared by unpaired t-test or nonparametric Mann-Whitney test depending on the outcome of tests for normality. Categorical data were assessed by chi-square test. Two-way repeated measures analysis of variance was used to evaluate main (time; group) and interaction effects (time x group) for clinical, laboratory and hemodynamic variables before and after tolvaptan therapy. Post hoc analysis was used for pre–post comparisons where either the main or the interaction effect was statistically significant. The area under the curve was calculated, and the optimal cut-off values of predictors of unsuccessful tolvaptan therapy were

determined. Univariate and multivariate binary logistic analyses with a forward stepwise procedure (P <0.10 for entry) were applied to assess the relationships between predictors of unsuccessful tolvaptan therapy and clinical variables. P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 17.0 J (SPSS Japan Institute, Tokyo, Japan).

Results

Clinical characteristics: Among all 60 patients, 18 (30%) had NYHA class IV HF symptoms, but none of them had orthopnea or severe hypoxemia with arterial oxygen saturation below 90% with oxygen supply via nasal cannula. The timing of tolvaptan administration was 3 (2-4) days after hospital admission. Of all 60 patients, 12 patients (20%) received short-term or transient intravenous therapies including with loop diuretics (6 patients), carperitide (8 patients) and/or dobutamine (1 patient) infusion either alone or in combination for the initial treatment of HF upon hospital admission, but all of them were successfully discontinued before tolvaptan therapy. Fifty-nine patients received 7.5 mg/day tolvaptan and only 1 patient received 15 mg/day tolvaptan. Among 18 patients with NYHA class IV HF symptoms, 61% were successfully treated with tolvaptan therapy. Of all 60 subjects, the majority (78%) were successfully treated (Group 1), but 13 patients (22%) were unsuccessfully treated with tolvaptan therapy (Group 2). Table 1 shows comparisons of the clinical characteristics between the two groups. The prevalence of patients with NYHA class IV, HF symptom score and heart rate were higher in Group 2 than in Group 1. Blood pressure levels were

similar in the two patient groups. Average dosages of furosemide-equivalent loop diuretics, enalapril-equivalent angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and carvediol-equivalent beta-blockers were similar in the two patient groups. The time intervals from hospitalization to initiation of tolvaptan therapy were similar in the two groups. Table 2 shows comparisons of laboratory, echocardiographic and hemodynamic parameters at baseline between the two groups. Group 2 had higher blood urea nitrogen, serum creatinine and plasma BNP and ANP levels than Group 1, whereas sodium concentrations, plasma arginine-vasopressin levels, plasma renin activity and plasma aldosterone concentration were similar in the two groups. Although the levels of urine osmolality were similar in the two groups, UNa/UCr and fractional excretion of sodium were lower in Group 2 than in Group 1. In contrast, UUN/UCr and fractional excretion of urine nitrogen were similar in the two groups. Group 2 had higher mean PCWP and mean RAP than Group 1 at baseline, whereas cardiac index and systemic vascular resistance index were similar in the two groups.

Effects of tolvaptan therapy on clinical, laboratory and hemodynamic parameters: Table 3 shows comparisons of the clinical effects of tolvaptan therapy between the two groups. Oral tolvaptan administration increased 24-hour urine volume at day 1 with no significant differences between the two groups. In addition, the averages of daily urine volume through days 1-7 were similar in the two groups (1987±890 and 1813±978 ml/day, p =ns). Body weight decreased in 94% of patients in Group 1 and 92% of patients in Group 2 seven days after the initiation of tolvaptan

therapy, with no significant differences between the two groups. However, HF symptom score improved and plasma natriuretic peptide level decreased only in Group 1. The changes in serum creatinine levels (interaction effect P =0.127) were not significantly different between the two groups. Three patients in Group 2 required additional interventions including intravenous infusion of inotropic agent and short-term ultrafiltration within 7 days after the initiation of tolvaptan therapy because of worsening of HF, and could not undergo follow-up hemodynamic measurement with right heart catheterization during tolvaptan therapy. In the other 57 patients, right heart catheterization was performed at a median of 7 (7-7) days after the initiation of tolvaptan therapy. Mean PCWP and mean RAP decreased only in Group 1, with a significant interaction effect (P <0.01, each), whereas cardiac index and systemic vascular resistance index were unchanged after tolvaptan therapy in both groups (Figure 1). After the short-term tolvaptan therapy, only 1 of 47 patients in the Group 1, but 12 out of 13 patients in the Group 2 required additional interventions including intravenous inotropic and/or carperitide therapy beyond simply holding oral diuretics during the hospital stay (Table 4). Hospital stay was significantly longer in Group 2 than in Group 1: 19 (17-27) vs. 45 (35-67) days, p <0.01.

Predictors of successful tolvaptan therapy: The results of univariate and multivariate logistic regression analyses evaluating the clinical, laboratory and hemodynamic risk factors for unsuccessful tolvaptan therapy are shown in Table 5. Multivariate logistic regression analysis showed that plasma BNP level was positively and UNa/UCr was negatively correlated to unsuccessful tolvaptan therapy.

In contrast, serum sodium level, eGFR, urine osmolality and all hemodynamic parameters were not independently correlated with clinical outcomes of short-term tolvaptan therapy. Receiver operating characteristic curve analysis showed that UNa/UCr best predicted unsuccessful tolvaptan therapy, with a cut-off value of 46.5 mEq/g·Cr with the area under the curve of 0.847 and the 95% confidence interval of 0.718-0.976 (sensitivity 77%, specificity 81%, positive predictive value 53%, negative predictive value 93% and accuracy 80%, P <0.01, Figure 2A), followed by plasma BNP level with a cut-off value of 778 pg/ml with the area under the curve of 0.786 and the 95% confidence interval of 0.651-0.920 (sensitivity 69%, specificity 81%, positive predictive value 50%, negative predictive value 90% and accuracy 78%, P <0.01). The combination of UNa/UCr <46.5 mEq/g·Cr and plasma BNP level >778 pg/ml predicted unsuccessful tolvaptan therapy with sensitivity of 54%, specificity 100%, positive predictive value 100%, negative predictive value 89% and accuracy 90% (Figure 2B). The results of univariate and multivariate linear regression analyses of variables associated with UNa/UCr are shown in Table 6. Plasma aldosterone concentration and dosage of oral furosemide were significantly and independently correlated with UNa/UCr.

Discussion

Tolvaptan therapy reduced body weight mainly via high-volume diuresis in almost all HF patients with volume overload in the present study. In addition, this therapy ameliorated HF symptoms and provided hemodynamic improvement in the majority of patients. However, about

20% of them were unsuccessfully treated, in whom 1) HF symptom score worsened or 2) there was the presence of a stationary HF symptom score ≥6 points, and mean PCWP >18 mmHg and mean RAP >10 mmHg, after tolvaptan therapy. Notably, the present study demonstrated that body weight reduction achieved by oral tolvaptan therapy itself was not always associated with symptom relief and sufficient hemodynamic improvement. We revealed that the combination of UNa/UCr and plasma BNP level best predicted clinically unsuccessful tolvaptan therapy.

Recent clinical reports have demonstrated that the early use of oral tolvaptan in patients with HF and overt volume overload can effectively reduce water retention via high-volume diuresis, which can minimize the need for continuous intravenous HF therapy and support early ambulation. Indeed, Suzuki et al. recently demonstrated that tolvaptan was as effective as and safer than intravenous carperitide, a natriuretic peptide, by head-to-head comparison in a Japanese population.[6] However, it has not been fully understood whether successful volume depletion with tolvaptan therapy always leads to the amelioration of patient symptoms and provides hemodynamic improvement,[13] especially in patients who are not concurrently treated with intravenous inotropic agents or intravenous diuretic/vasodilation therapy. In addition, it has not been elucidated how we can predict patients who will be or not be successfully treated with oral tolvaptan administration alone. Almost all patients achieved body weight reduction mainly via high-volume diuresis, and about 80% of all patients were clinically successfully treated with oral tolvaptan therapy. Notably, about 60% of patients with ambulatory NYHA class IV were successfully treated with oral tolvaptan

administration alone. However, about 20% of all patients had an unsuccessful clinical course during oral tolvaptan therapy despite achieving similar urine volume increment and body weight reduction to those with successful clinical outcomes. On the basis of these observations, tolvaptan can induce forced diuresis in the majority of HF patients unless they present with non-ambulatory NYHA class IV or cardiogenic shock; however, forced diuresis itself may not always result in sufficient cardiorenal hemodynamic improvement or symptom relief. Indeed, patients who were unsuccessfully treated with tolvaptan therapy did not show any improvements in hemodynamic parameters and HF symptom scores as well as plasma natriuretic peptide levels. Therefore, it is very important to identify the risks for unsuccessful oral tolvaptan therapy in order to develop personalized treatment plans. Patients who were unsuccessfully treated with tolvaptan therapy had clinical conditions with severely decompensated HF and might have required prompt and specific cardiorenal support mainly with intravenous inotropic and/or carperitide therapy concomitantly with aquaretic therapy upon hospital admission.

We revealed that first-morning spot UNa/UCr best predicts successful tolvaptan therapy in patients with HF and clinical evidence of volume overload. Since UCr is inversely proportional to urine flow rate, UNa/UCr accounts for variations in urine flow rate,[17] assuming no effect of urine flow rate on urine sodium excretion. HF-related relative arterial underfilling is an important signal that triggers sodium and water retention.[18-20] It stimulates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), which largely contribute to renal tubular sodium

reabsorption to maintain an effective arterial blood volume. In a clinical setting, loop diuretic-induced sodium loss in the daytime without sufficient RAAS blockade may further augment renal tubular sodium reabsorption at night. Indeed, plasma aldosterone concentration and the dosage of furosemide were independently associated with first-morning spot UNa/UCr. Interestingly, fractional excretion of urine nitrogen, a marker of prerenal azotemia, was similar in the two groups. Therefore, we speculate that low first-morning spot UNa/UCr is a clinical indicator of intrinsic RAAS/SNS activation secondary to arterial underfilling rather than true hypovolemia. The combination of BNP, which reflects the severity of ventricular overload, and UNa/UCr provided further improvement of accuracy in the prediction of clinically unsuccessful tolvaptan therapy. Low UNa/UCr and high plasma BNP levels may reflect HF-related arterial underfilling and compensatory processes of maximal renal tubular sodium reabsorption despite excessive cardiac overload, indicating severe decompensated HF. In such clinical conditions, forced diuresis by tolvaptan may augment renal underfilling and may result in insufficient cardiorenal hemodynamic improvement.

Right heart catheterization-derived intra-cardiac pressure did not decrease only in the patient group who were unsuccessfully treated with tolvaptan therapy, despite being a significant weight reduction. Therefore, we speculate that the central fluid shift from the venous capacitance vessels of the splanchnic circulation may play a role in persistent excessive cardiac preload in such patients via the activation of RAAS and SNS.[21] Large numbers of α1 and α2 adrenergic receptors are present in the splanchnic veins, making them highly sensitive to stimulation by the SNS.[21] Although the

dosages of ACEI/ARB and beta blockers were similar in the two patient groups, sufficient dosages of these medications for effectively regulating RAAS and SNS can vary individually depending on their clinical conditions including HF severity and the presence of coexisting disorders. Intrinsic RAAS and SNS might be much more activated and/or insufficiently inhibited at baseline in patients who were not successfully treated with tolvaptan while plasma levels of renin activity and aldosterone were not statistically different between the two groups. The mechanisms underlying discrepancy between the changes in body fluid and hemodynamic status warrant further investigation.

Potential limitations of the present study include the small sample population and the heterogeneous etiologies of HF with retrospective evaluation. Further studies with larger populations are needed to specify the etiological differences that might contribute to the effectiveness of tolvaptan therapy. Patients who required cardiac intensive care because of "non-ambulatory" NYHA class IV HF including cardiogenic shock were not included in the present study. In addition, as a single-center study with no control group for comparison, the generalizability of the present results is limited. Recent clinical observations including post-marketing survey demonstrated that about 20% of patients received intravenous carperitide infusion concomitantly with oral tolvaptan therapy.[4)] However, carperitide was not concomitantly administered with tolvaptan therapy in all patients in the present study. Three out of 13 patients in Group 2 required additional interventions including intravenous infusion of inotropic agent and short-term ultrafiltration within 7 days after the initiation of tolvaptan therapy because of worsening of HF; therefore, the post-treatment data including the HF

score, urine volume, body weight, renal function and neurohumoral parameters in Group 2 can be influenced by these therapies. Although almost all patients received therapy of 7.5 mg of tolvaptan daily, dose effects of this compound should be investigated further. Plasma levels of angiotensin II and catecholamines, which can mainly and directory contribute to renal tubular sodium reabsorption and the tones of venous capacitance vessels of the splanchnic circulation to maintain an effective arterial blood volume, were not measured in the present study. The long-term effects of tolvaptan therapy in clinical responders in this population were not tested in the present study. Finally, the effects of tolvaptan treatment in patients with moderate to severe renal dysfunction warrant further evaluation.[22)]

Conclusions: Tolvaptan therapy provided body weight reduction mainly via high-volume diuresis in most patients, and about 80% of them were identified as clinical responders. However, this therapy was insufficient for symptom relief and hemodynamic improvement in the minority of patients. The combination of low UNa/UCr <46.5 mEq/g·Cr and high plasma BNP >778 pg/ml can effectively predict successful tolvaptan therapy, and the measurements of these parameters that are easily performed by routine tests can help clinicians tailor HF treatment.

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Disclosures

Competing interests: K.D. received lecture fees of equal to or more than 500,000 yen from Otsuka Pharma Inc. in 2014. N.Y. received lecture fees of more than 500,000 yen from Daiichi Sankyo Co. Ltd. and Astellas Pharma Inc. in 2014. M.I. received lecture fees of more than 500,000 yen from Daiichi Sankyo Co. Ltd. in 2014. M.I. received a single-year unrestricted research grant for the Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, of equal to or more than 2 million yen, from Astellas Pharma Inc., Pfizer Inc., Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd. and Public Health Research Foundation in 2014.

No relevant conflicts of interest were disclosed by the authors.

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Figure Legends

Figure 1. Comparisons of hemodynamic parameters at baseline and after tolvaptan treatment in Group 1 (blue circle) and Group 2 (red circles). PCWP, pulmonary capillary wedge pressure; RAP, right arterial pressure; SVRI, systemic vascular resistance index; CI, cardiac index. Blue and red boxes indicate Groups 1 and 2, respectively. *P <0.05 versus baseline.

Figure 2. (A) The receiver operating characteristic identifying cut-off values (arrows) of UNa/UCr (blue line) and plasma BNP level (red line) for the prediction of unsuccessful tolvaptan therapy, and (B) scatter plots of UNa/UCr and plasma BNP levels in patients in Group 1 (blue circle) and Group 2 (red circles).

Table 1. Baseline Clinical Characteristics

	All (n =60)	Group 1 (n =47)	Group 2 (n =13)	P value
Demographic parameters				
Male, %	77	77	77	0.980
Age, years	70 ± 11	71 ± 11	66 ± 11	0.209
NYHA IV, n (%)	18 (30)	11 (23)	7 (54)	0.036
HF symptom score	6.5 ± 1.3	6.2 ± 1.4	7.3 ± 0.8	0.006
Body weight, kg	63.1 ± 14.1	62.0 ± 13.7	67.2 ± 14.8	0.132
Systolic blood pressure, mmHg	115 ± 23	117 ± 24	109 ± 20	0.346
Heart rate, bpm	74 ± 13	71 ± 12	82 ± 14	0.009
Daily urine volume, ml/day	1410 ± 915	1511 ± 953	1023 ± 592	0.049
Daily water intake, ml/day	731 ± 274	749 ± 292	665 ± 183	0.341
Ischemic etiology, %	37	31	38	0.621
Atrial fibrillation, %	52	53	46	0.656
Medication				
ACEI/ARB, %	88	91	77	0.151
Enalapril-equivalent doses, mg	5 (5-10)	5 (5-10)	5 (5-10)	0.434
Beta-blockers, %	58	57	62	0.793
Carvedilol-equivalent doses, mg	2.5 (0-5)	2.5 (0-5)	2.5 (0-5)	0.895
Loop diuretics, %	97	96	100	0.453
Furosemide-equivalent doses, mg	40 (20-60)	40 (20-60)	60 (20-80)	0.261
Thiazide diuretics, %	10	11	8	0.756
Aldosterone antagonists, %	58	60	54	0.713
Oral inotropic agents, %	5	4	8	0.618
Tolvaptan Therapy				
Time from hospital admission, day	3 (2-4)	3 (2-4)	3 (2-4)	0.860

	2			
Time from oral to RHC, day	7(7-7)	7(7-7)	7(7-8)	0.221
Duration, day	10 (7-19)	8 (7-15)	17 (8-45)	0.010
Outcome				
Hospitalization, day	23 (17-35)	19 (17-27)	45 (35-67)	<0.001

NYHA, New York Heart Association; HF, heart failure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Laboratory, Echocardiographic and Hemodynamic Parameters

	All (n =60)	Group 1 (n =47)	Group 2 (n =13)	P value
Laboratory parameters				
Blood urea nitrogen, mg/dl	29 ± 15	27 ± 15	35 ± 14	0.040
Serum creatinine, mg/dl	1.37 ± 0.68	1.29 ± 0.62	1.64 ± 0.80	0.043
eGFR, ml/min/1.73m^2	46 ± 19	49 ± 18	38 ± 16	0.088
Serum sodium, mEq/l	138 ± 5	138 ± 4	136 ± 6	0.318
Serum potassium, mEq/l	4.1 ± 0.6	4.1 ± 0.5	4.0 ± 0.8	0.498
Serum osmolality, mOsm/kgH_2O	289 ± 11	289 ± 10	289 ± 12	0.781
Plasma BNP, pg/ml	629 ± 508	501 ± 389	1094 ± 607	0.002
Plasma ANP, pg/ml	190 ± 156	169 ± 152	266 ± 143	0.025
Plasma arginine-vasopressin, pg/ml	7.0 ± 7.0	7.2 ± 7.6	6.6 ± 4.2	0.627
Plasma renin activity, ng/ml/h	5.5 ± 6.5	5.6 ± 6.7	5.4 ± 5.7	0.651
Plasma aldosterone, pg/ml	109 ± 105	105 ± 98	124 ± 127	0.848
Urine osmolality, mOsm/kgH_2O	442 ± 147	436 ± 151	464 ± 129	0.499
UNa/UCr, mEq/g·Cr	104 ± 79	121 ± 79	44 ± 40	<0.001
UUN/UCr, mg/g·Cr	6.6 ± 2.5	6.6 ± 2.7	6.5±1.7	0.770
Fractional excretion of sodium, %	1.1 ± 1.5	1.3 ± 1.6	0.6 ± 0.5	0.023
Fractional excretion of urine nitrogen, %	33 ± 16	33 ± 17	30 ± 8	0.453
Echocardiographic parameters				
Left ventricular diastolic diameter, mm	60 ± 13	60 ± 11	62 ± 17	0.700
Ejection fraction, %	40 ± 19	41 ± 18	36 ± 21	0.309
Hemodynamic parameters				
Mean RAP, mmHg	12 ± 5	11 ± 5	16 ± 5	0.006
Systolic PAP, mmHg	50 ± 15	48 ± 15	54 ± 13	0.175
Mean PCWP, mmHg	24 ± 7	23 ± 8	28 ± 5	0.008

Cardiac index, l/min/m^2	2.4 ± 0.7	2.4 ± 0.7	2.2 ± 0.7	0.216
Systemic vascular resistance index, dynes/sec/cm^{-5}/m^2	2678 ± 1040	2654 ± 962	2779 ± 1316	0.726

eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; UNa/UCr , urine sodium/creatinine ratio; UUN/UCr , urine urea nitrogen/creatinine ratio; RAP, right atrial pressure; PAP, pulmonary artery prresure; PCWP, pulmonary capillary wedge pressure.

Table 3. Clinical Effects of Tolvaptan Therapy

	Group 1 (n =47)	Group 2 (n =13)	Group effect P	Time effect P	Interaction effect P
Daily urine volume, ml/day					
Baseline (day 0)	1511±957	1023±592	0.146	<0.001	0.904
Post-treatment (day 1)	2315±1523*	1786±1106*			
Daily water intake, ml/day					
Baseline (day 0)	749±292	665±183	0.332	0.002	0.799
Post-treatment (day 1)	1114±726*	973±283			
Body weight, kg					
Baseline (day 0)	62.0±13.7	67.2±14.8	0.228	<0.001	0.714
Post-treatment (day 7)	59.6±13.5*	64.8±13.7*			
HF symptom score					
Baseline (day 0)	6.2±1.4	7.3±0.8	<0.001	<0.001	<0.001
Post-treatment (day 7)	2.8±1.0*	6.9±0.8			
Blood urea nitrogen, mg/dl					
Baseline (day 0)	27±15	35±14	0.293	0.087	0.044
Post-treatment (day 7)	32±16*	35±20			
Serum creatinine, mg/dl					
Baseline (day 0)	1.29±0.62	1.64±0.80	0.201	0.121	0.127
Post-treatment (day 7)	1.39±0.74	1.64±0.92			
Serum sodium, mEq/l					
Baseline (day 0)	138±4	136±6	0.214	0.137	0.889
Post-treatment (day 7)	139±4	137±6			
Plasma BNP, pg/ml					

Baseline (day 0)	501±389	1094±607	<0.001	0.182	0.016
Post-treatment (day 7)	350±317*	1138±493			
Plasma ANP, pg/ml					
Baseline (day 0)	169±152	266±143	0.004	0.642	0.002
Post-treatment (day 7)	126±188*	329±179*			

*P <0.05 versus baseline

HF, heart failure; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide

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Table 4. Details of Additional Therapy for Patients in the Group 2

No	Age	HF symptom score	Intervention
1	77	7	Ultrafiltration
2	80	7	Dobutamine + Carperitide
3	57	8	Carperitide
4	47	8	Milrinone + Furosemide
5	55	8	Dobutamine + Carperitide + Furosemide
6	50	8	Dobutamine + Milrinone + Carperitide
7	69	7	Dobutamine + Carperitide + Catheter ablation for atrial flutter
8	56	5	Dobutamine
9	81	7	Dobutamine + Carperitide + Furosemide
10	75	7	Dobutamine + Carperitide
11	70	7	Dobutamine + Ultrafiltration
12	64	8	Landiolol + Furosemide
13	78	7	None

HF, heart failure.

Table 5. Univariate and Multivariate Logistic Regression Analyses of the Factors for Unsuccessful Tolvaptan Therapy

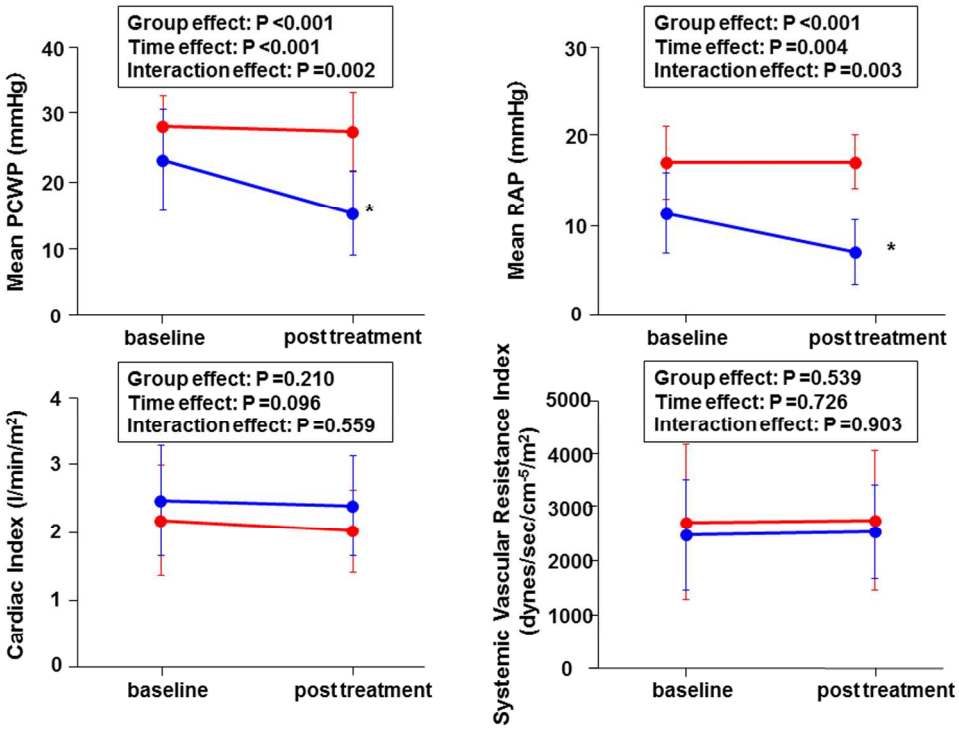
	Univariate		Multivariate	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
NYHA, class	3.784 (1.230-11.645)	0.003		
HF symptom score	2.447 (1.195-5.012)	0.014		
Dosage of loop diuretics, mg	1.016 (0.996-1.036)	0.113		
Dosage of furosemide, mg	1.019 (0.994-1.044)	0.144		
eGFR, ml/min/1.73 m^2	0.967 (0.931-1.005)	0.086		
Serum sodium, mEq/l	0.931 (0.825-1.050)	0.245		
Plasma BNP, pg/ml	1.002 (1.001-1.004)	0.002	1.003 (1.001-1.006)	0.005
Plasma ANP, pg/ml	1.004 (1.000-1.008)	0.072		
Plasma arginine-vasopressin, pg/ml	0.986 (0.895-1.087)	0.781		
Plasma renin activity, ng/ml/h	0.995 (0.901-1.099)	0.916		
Plasma aldosterone, pg/ml	1.002 (0.996-1.007)	0.574		
Urine osmolality, mOsm/kgH_2O	1.001 (0.997-1.006)	0.547		
UNa/UCr, mEq/g·Cr	0.971 (0.950-0.992)	0.007	0.959 (0.929-0.990)	0.009
Fractional excretion of sodium, %	0.330 (0.093-1.171)	0.086		
Ejection fraction, %	0.986 (0.952-1.020)	0.408		
Mean RAP, mmHg	1.200 (1.047-1.375)	0.009		
Mean PCWP, mmHg	1.088 (0.999-1.185)	0.052		
Cardiac index, l/min/m^2	0.599 (0.232-1.546)	0.289		

NYHA, New York Heart Association; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; UNa/UCr, urine sodium/creatinine ratio; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure

Table 6. Univariate and Multivariate Linear Regression Analyses of Variables Associated with UNa/UCr

	Univariate		Multivariate	
	Coefficients	P value	β-coefficients	P value
NYHA, class	-0.039	0.768		
HF symptom score	-0.095	0.469		
Dosage of loop diuretics, mg	0.032	0.810		
Dosage of furosemide, mg	-0.345	0.007	-0.322	0.009
eGFR, ml/min/1.73 m^2	-0.238	0.066		
Serum sodium, mEq/l	0.407	0.001		
Plasma BNP, pg/ml	-0.024	0.854		
Plasma ANP, pg/ml	0.016	0.905		
Plasma arginine-vasopressin, pg/ml	0.035	0.798		
Plasma renin activity, ng/ml/h	-0.216	0.104		
Plasma aldosterone, pg/ml	-0.388	0.003	-0.390	0.002
Ejection fraction, %	0.388	0.003		
Mean RAP, mmHg	0.011	0.935		
Mean PCWP, mmHg	-0.209	0.109		
Cardiac index, l/min/m^2	0.159	0.226		

UNa/UCr, urine sodium/creatinine ratio; NYHA, New York Heart Association; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure



Comparisons of hemodynamic parameters
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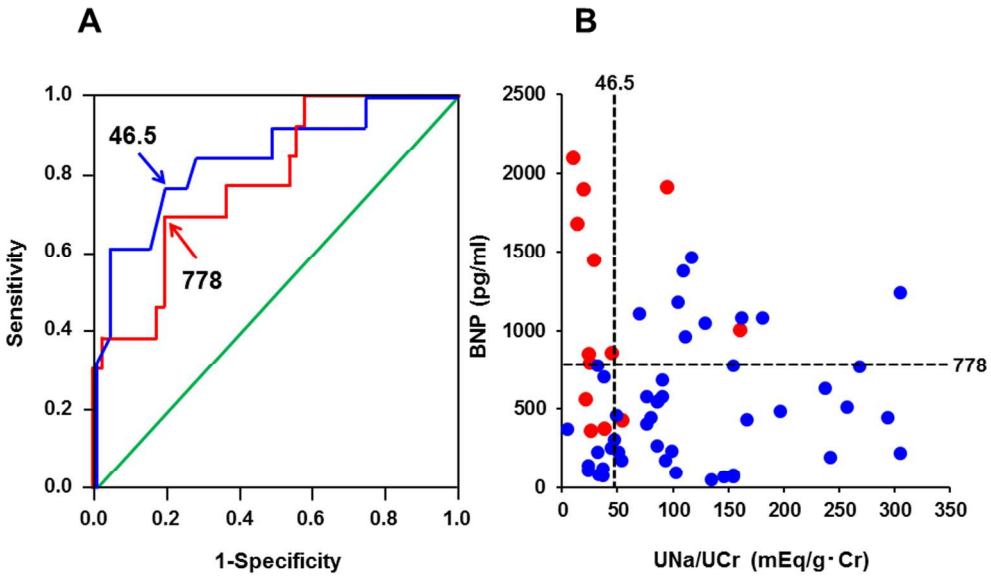

UNa/UCr and plasma BNP in the prediction of clinically unsuccessful tolvaptan therapy
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