Original Article

Clinical Characteristics of Responders to Treatment with Tolvaptan in Patients with Acute Decompensated Heart Failure: Importance of Preserved Kidney Size

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Short title: Clinical Characteristics of Responders to Tolvaptan

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Key Words: heart failure, vasopressin, kidney size

Total word count: 4293 words, 4 figures and 2 tables

ABSTRACT

Background: Recent clinical trials have demonstrated the efficacy of short-term treatment with tolvaptan, an oral vasopressin V2 receptor antagonist, in patients with heart failure. However, the response to tolvaptan varies among patients. The aim of this study was to determine factors associated with response to tolvaptan in patients with acute decompensated heart failure (ADHF).

Methods: The Tolvaptan Registry, a prospective, observational, multicenter cohort study performed in Japan, aims to determine factors affecting the responsiveness of tolvaptan in patients with ADHF. We enrolled ADHF patients treated with tolvaptan and they were divided into two groups: responders and non-responders. Responders were defined as subjects who met all of the following three conditions: (1) increasing urine volume during a 24-hour period after the start of tolvaptan treatment, (2) improvement in NYHA functional class and (3) decrease in cardiothoracic ratio assessed by chest X-ray on day 3 of tolvaptan administration.

Results: Among the 114 patients, treatment with tolvaptan improved three conditions of heart failure (increase in urine volume, improvement in NYHA functional class and decrease in cardiothoracic ratio) in more than half of the patients with ADHF (number of responders versus non-responders: 71 (62%) versus 43 (38%)). As for baseline characteristics, estimated glomerular filtration rate, urine osmolality, and kidney size were significantly greater in responders than in non-responders. Multivariate logistic analysis revealed that kidney size was independently associated with responders.

Conclusions: The main clinical characteristic of responders to treatment with tolvaptan is that kidney size is preserved.

Introduction

Heart failure (HF) is characterized by fluid overload. Non-potassium-sparing diuretics including loop and thiazide diuretics are used for treatment of fluid overload. However, natriuretic therapy alone is sometimes insufficient to control fluid retention [1]. Furthermore, it leads to activation of neurohormones and serum electrolyte depletion. Tolvaptan is an oral vasopressin V2 receptor antagonist. Recent clinical trials have demonstrated that short-term treatment with tolvaptan in addition to standard therapy including diuretics increased urine volume, decreased body weight and improved many heart failure symptoms in patients with acute decompensated heart failure (ADHF) [2-5]. Thus, treatment with tolvaptan is expected to be helpful in reducing the length of hospital stay.

However, the response to tolvaptan varies among patients and is sometimes unpredictable [6, 7]. Imamura et al showed that urine osmolality can predict increase in 24-h urine volume after treatment with tolvaptan in patients with ADHF [7, 8]. We should consider the renal function or reserve in predicting the response to tolvaptan. Serum creatinine or estimated GFR (eGFR), however, is not sufficient for predicting responders in HF patients [7, 8]. Tubular mechanisms are also important to enhance water retention during HF [9]. Aldosterone activates sodium-retaining channels in the collecting tubule, and arginine vasopressin via the V2 receptor promotes water reabsorption by inserting aquaporin-2 water channels into the luminal membrane of the collecting tubule. Moghazi et al. showed that kidney size is inversely correlated with glomerular sclerosis and tubular atrophy. Kidney size is one of the simple estimates of renal reserve and function of collecting tubules [10].

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The aim of this study was to determine the characteristics of responders to tolvaptan in patients with ADHF by use of variables including new factors.   We re-defined a responder based on both acute urine response and remission of HF-related symptoms and signs, since an improvement in HF-related symptom or signs is another therapeutic target in the treatment of ADHF.   We investigated multiple variables in patients with ADHF, including creatinine, eGFR, urine osmolality, blood pressure, and left ventricular ejection fraction (LVEF) and kidney size which evaluate the presence or absence of renal atrophy.

Materials and methods

Patient population

The Tolvaptan Registry, a prospective, observational, multicenter cohort study performed in Japan, aims to determine factors affecting the responsiveness of tolvaptan in patients with ADHF.   The Tolvaptan Registry enrolled ADHF patients treated with tolvaptan from August 2011 to December 2013 in 7 hospitals throughout Japan.   We retrospectively analyzed data from the Tolvaptan Registry and evaluated the effectiveness of tolvaptan in ADHF patients.

All of the patients had evidence of pulmonary congestion or pleural effusion on chest X-rays and symptoms of heart failure corresponding to NYHA functional classes II to IV.   In the present study, we enrolled patients who underwent thoracic and abdominal multi detector-row computed tomography (MDCT).   We excluded patients who did not undergo MDCT (Exclusion 1, Fig. 1).   Indications for CT examinations are stated in practice parameters of American College of Radiology and we performed MDCT according to the statements[11].   Thoracic MDCT was performed to screen for pneumonia, pleural effusion and calcification of the coronary artery.   The reasons for performing abdominal MDCT were

not for evaluation of kidney size but for clarification of findings from laboratory abnormalities, evaluation of abdominal fluid collections and assessment of abnormalities of abdominal or pelvic vascular structures[11].   We excluded patients who had severe hypotension (supine systolic blood pressure (SBP) < 80 mmHg) and who were treated with hemofiltration or dialysis.   Patients with acute coronary syndrome were also excluded (Exclusion 2, Fig. 1).   Furthermore, we excluded patients for whom the dose of tolvaptan was changed during a period of 3 days after the start of tolvaptan treatment and patients for whom the doses of diuretics except for tolvaptan were changed during a period of 24 h after the start of tolvaptan treatment (Exclusion 2, Fig. 1).   The present study complied with the Declaration of Helsinki, and the institutional review board of Okayama University Graduate School of Medicine approved the research protocol [the application number 449].   Informed consent was obtained from all patients before enrollment.

Study protocols

The initial tolvaptan dose was 3.75 mg to 15 mg/day, and the same dose of tolvaptan was maintained for 3 days.   Baseline clinical data were obtained within 24 h before administration of tolvaptan. LVEF was assessed by transthoracic echocardiography [12], and eGFR was determined by the modified Modification of Diet and Renal Disease study formula (MDRD) for Japanese: eGFR= $194 \times (\text{age}^{-0.287}) \times (\text{serum creatinine}^{-1.094}) \times (0.739$ if female) [13].   To assess kidney size, we measured the longest longitudinal length of the kidney on each side in coronal section images of MDCT before tolvaptan administration. We defined kidney size as the mean longitudinal length on the two sides (Fig. 2).   Clinical assessments consisting of urine volume, body weight, NYHA class, markers of renal function and electrolytes and cardiothoracic ratio assessed by chest X-ray were performed before and 3

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days after tolvaptan administration.　In this study, chest X-rays were taken in the supine or sitting position at end-inspiration.　Comparisons were made for patients in the same conditions.　During tolvaptan administration, patients were allowed to drink water freely. Urine volume was measured every 24 hours during tolvaptan administration.

Definition of responders

Patients were classified into two groups: responders and non-responders. Responders were defined as subjects who met all of the following three conditions: (1) increasing urine volume during a 24-hour period after the start of tolvaptan treatment, (2) improvement in New York Heart Association (NYHA) functional class and (3) decrease in cardiothoracic ratio assessed by a chest X-ray on day 3 of tolvaptan administration.　In all of the patients included in this study, fluid retention was one of the causes of heart failure, and diuretics were necessary for reduction of fluid retention.　Fluid retention causes enlargement of the right-side heart and increase in CTR.　It has been reported that CTR reflected right-sided rather than left-sided cardiomegaly [13].　Other investigators have reported that high CTR at baseline as measured by a chest x-ray was a marker of poor prognosis [14]. Therefore, reduction of CTR indicates reduction of fluid in the body and contributes to improvement in prognosis.　We therefore used CTR as one of the definitions of responder.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, USA).　All data are expressed as mean ± standard deviation (SD) and the mean differences between groups were analyzed using Student's t-test. Proportional differences were analyzed using Fisher's exact analysis.　Categorical variables were analyzed using the

chi-squared test.   We conducted one-way analysis of variance (ANOVA) by considering data multiplicity over time, and used Wilcoxon's signed rank test to compare NYHA before treatment and that after treatment.   We calculated odds ratios (OR) derived from the logistic regression model to predict responders.   All baseline variables were included in logistic regression analyses.   Multivariate analysis was performed using all variables with $P<0.05$ in univariate analysis.   A P value of <0.05 was considered significant.

Results

Effects of tolvaptan

Of the 159 patients registered in the Tolvaptan Registry, a total of 45 patients were excluded from this analysis because of insufficient data collection or exclusion criteria (Fig. 1).   Data for 114 patients were analyzed in this study (Table 1 and Figs. 1 and 3).   More than half of the patients with ADHF were responders (number of responders: 71 (62%)). We analyzed the overall effects of tolvaptan on the three conditions to clarify the details of the effect on each condition.

Urine volume: The urine volume in 16 of the 114 patients did not increase (Fig. 3), but the mean urine volume significantly increased on day 1 of tolvaptan administration in both groups (71 responders, day 0: 1274±646 versus day 1: 2627±1040 mL, P<0.001; 43 non-responders, day 0: 1302±721 versus day 1: 1996±889 mL, P<0.05) (Fig. 4A).   However, the urine volume for each of the 3 days was significantly greater in responders than in non-responders (day 1, responders versus non-responders: P<0.005; day 2, responders: 2531±1033 versus non-responders: 1960±1011 mL, P<0.01; day 3, responders: 2259±818 versus non-responders: 1838±869 mL, P<0.05).   Body weight reductions from day 0 to 3 were significantly greater in responders than in non-responders (responders: -2.2±1.7 versus

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non-responders: -0.7±1.6 kg, P<0.001).

NYHA class: NYHA class did not improve in 16 of the 98 patients with increasing urine volume (Fig. 3).   Therefore, the condition of increasing urine volume is not sufficient to define responders to tolvaptan in a clinical setting. In addition to increase in urine volume, improvement of heart failure symptoms including improvement in NYHA functional class or signs such as decrease in cardiothoracic ratio is important in treatment of ADHF. Improvements in mean NYHA class in responders and non-responders are shown in Fig. 4B. NYHA class did not change in 22 of the 43 non-responders (Fig. 4B), but median NYHA class was significantly decreased on day 3 of tolvaptan administration in both groups (responders, day 0: 3.2±0.6 versus day 3: 2.2±0.5, P<0.001; non-responders, day 0: 3.1±0.6 versus day 3: 2.6±0.6, P<0.05).   Finally, NYHA class was significantly lower in responders than in non-responders on day 3 of tolvaptan treatment (responders: 2.2±0.5 versus non-responders: 2.6±0.6, P<0.001).

Cardiothoracic ratio: As shown in Fig. 4C, cardiothoracic ratio in responders was significantly decreased after tolvaptan treatment, but it was not decreased in non-responders (responders, day 0: 65±6 versus day 3: 61±6, P<0.0001; non-responders, day 0: 61±5 versus day 3: 67±6, P=NS).   Finally, cardiothoracic ratio was significantly lower in responders than in non-responders on day 3 of tolvaptan treatment (responders versus non-responders on day 3, P<0.0001).

Baseline characteristics according to responsiveness to treatment with tolvaptan

As shown in Table 1, there were no significant differences between responders and non-responders in baseline characteristics including age, sex, BMI, SpO$_2$, NYHA functional class, cardiothoracic ratio, LVEF, underlying heart diseases, medical history and laboratory

parameters such as serum C-reactive protein, hemoglobin, uric acid, serum sodium, plasma BNP levels.   There were also no significant differences in the doses of tolvaptan between responders and non-responders.   As for laboratory parameters concerning kidney function, there were significant differences in serum BUN, serum creatinine, eGFR, and urine osmolality between the two groups.   Kidney size assessed by longitudinal length of the kidney (Fig. 2) was significantly greater in responders than in non-responders (longitudinal kidney size of responders versus non-responders: 9.3±1.1 versus 8.3±1.2 cm, P<0.001).

The doses of diuretics except for tolvaptan were not changed during a 24-hour period after the start of tolvaptan treatment, because the chief purpose of this study was to evaluate the effectiveness of tolvaptan.   In cases of increasing urine volume on the first day, the doses of other diuretics were not changed for three days.   Patients who showed no increase in urine volume in the first 24 hours were categorized as non-responders.   In non-responders, the doses of other diuretics were probably increased 24 hours later according to the judgment of each medical doctor.   However, changes in doses of other diuretics were unknown, and change in dose did not contribute to the results of this study.

Independent predictors of responsiveness to treatment with tolvaptan

Results of univariate and multivariate linear regression analyses of factors associated with responders to treatment with tolvaptan are shown in Table 2. In univariate analysis, age, eGFR and kidney size were significantly associated with responders. Moreover, multivariate logistic analysis revealed that kidney size (OR: 1.083, P=0.001, 95% CI [1.031-1.137]) was an independent determinant of responders.

Discussion

There were three major findings in the present study.   First, treatment with tolvaptan improved three conditions of heart failure (increase in urine volume, improvement in NYHA functional class and decrease in cardiothoracic ratio) in more than half of the patients with ADHF.   Second, eGFR, urine osmolality and kidney size were significantly greater in responders to tolvaptan than in non-responders.   Third, multivariate logistic analysis revealed that kidney size was independently associated with responders.   These findings indicate that treatment with tolvaptan for ADHF is effective in patients with preserved kidney size.

In a stable hemodynamic state, eGFR level is a good parameter for renal function. However, in the ADHF period, eGFR level may not accurately reflect renal function.   For example, fluid retention causes a higher eGFR level than the original value, whereas a decrease in blood pressure causes a lower eGFR level than the original value [15]. Measurement of kidney size is a method for morphologic evaluation, and an atrophic kidney suggests progressive renal failure.

Kidney size is influenced by various factors including age, sex, right and left sides, BMI and absence or presence of hypertension and diabetes mellitus [14, 15].   In this study, univariate and multivariate analyses revealed that kidney size was an independent determinant of responders.   The mean values of normal kidney sizes assessed by longitudinal lengths in Japanese are 9.8 cm on the right side and 10.6 cm on the left side [16].   Since kidney size in non-responders to tolvaptan was 8.3±1.2 cm, their kidneys were slightly atrophic.   On the other hand, kidney size in responders to tolvaptan was 9.3±1.1 cm.   It has been reported that kidney size is correlated to renal function [10].   These results indicate that treatment with tolvaptan for ADHF is effective in patients with preserved kidney size, which implies preserved renal reserve and function of collecting tubules.   Tolvaptan was not effective for

patients with atrophic kidneys.   Furthermore, this study showed that measurement of kidney size by computed tomography is a simple method and provides important information including information for predicting responders to tolvaptan.

Imamura et al. reported that maintained urine osmolality before administration of tolvaptan and decrease in urine osmolality after 4-6 hours of tolvaptan administration predict responders [7, 8].   In their study, responders were defined as patients with an increase in urine volume during the first 24 h after the start of administration.   In our study, baseline urine osmolality was also significantly higher in responders than in non-responders, and eGFR was higher in responders than in non-responders.   These results indicate that maintained renal function including capacity of filtration and urinary concentraion is an important factor for response to tolvaptan.

We defined responders on the basis of acute urine response and remission of heart failure symptoms and signs assessed by NYHA functional class and chest X-ray.   NYHA class did not improve in 16 of the 98 patients with increasing urine volume.   Therefore, increase in urine volume is not sufficient to define responders to tolvaptan in a clinical setting. Furthermore, to prevent adverse effects such as thirst and hypernatremia, it is necessary to observe patients treated with tolvaptan without water restriction.   Thus, urine volume is affected by the quantity of water intake.   Therefore, we think it is not sufficient to evaluate responder only by increasing urine volume.   We considered CTR as an index of intravascular fluid volume or congestion, and it might be better to definite responders on the basis of decrease in body weight or decrease in IVC diameter or transtricuspid pressure gradient measured by echocardiography.   Further studies are needed to clarify this point.

Study limitations

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The present study has several limitations.   First, since other therapeutic agents including an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker and a β blocker were used [17, 18], the efficacy of tolvaptan alone could not be precisely evaluated.   Second, kidney size is influenced by various factors including age, sex, right and left sides, BMI and absence or presence of hypertension and diabetes mellitus [14, 15]. Therefore, it was necessary to perform univariate and multivariate analyses including factors related to kidney size.   In our study, we measured kidney size by means of computed tomography; however, in terms of radiation exposure, this approach does not seem to be reimbursable.   Ultrasound should be the first choice because it involves no radiation exposure.   Third, we included ADHF patients who underwent CT at index admission.   This is one of the selection biases and had the possibility of influencing the results.   Fourth, the dose of tolvaptan was determined by each doctor, and we therefore could not rule out the possibility that the dose of tolvaptan was not sufficient in non-responders.   We can only state that there was no significant difference in the dose of tolvaptan between responders and non-responders in this study.

A different study design, a larger prospective study, and matching by propensity score for estimation of kidney size are needed to confirm the predictors of tolvaptan effectiveness.

Conclusions

Treatment with tolvaptan for ADHF is effective in more than half of the patients. Kidney size was significantly greater in responders to tolvaptan than in non-responders and it was independently associated with responders.   Treatment with tolvaptan for ADHF was effective in patients with preserved kidney size, which implies preserved renal reserve and

function of collecting tubules.

Conflict of Interest: none declared

References

[1]　JCS-Joint-Working-Group. Guidelines for Treatment of Acute Heart Failure (JCS 2011). Circ J 2013;77:2157-201.

[2]　Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, Orlandi C. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;107:2690-6.

[3]　Gheorghiade M, Konstam MA, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332-43.

[4]　Inomata T, Izumi T, Matsuzaki M, Hori M, Hirayama A. Phase III clinical pharmacology study of tolvaptan. Cardiovasc Drugs Ther 2011;25 Suppl 1:S57-65.

[5]　Watanabe K, Dohi K, Sugimoto T, Yamada T, Sato Y, Ichikawa K, Sugiura E, Kumagai N, Nakamori S, Nakajima H, Hoshino K, Machida H, Okamoto S, Onishi K, Nakamura M, Nobori T, Ito M. Short-term effects of low-dose tolvaptan on hemodynamic parameters in patients with chronic heart failure. J Cardiol 2012;60:462-9.

[6]　Robertson GL. Vaptans for the treatment of hyponatremia. Nat Rev Endocrinol 2011;7:151-61.

[7]　Imamura T, Kinugawa K, Shiga T, Kato N, Muraoka H, Minatsuki S, Inaba T, Maki H, Hatano M, Yao A, Kyo S, Nagai R. Novel criteria of urine osmolality effectively predict response to tolvaptan in decompensated heart failure patients--association between non-responders and chronic kidney disease. Circ J 2013;77:397-404.

[8]　Imamura T, Kinugawa K, Minatsuki S, Muraoka H, Kato N, Inaba T, Maki H, Shiga T,

Hatano M, Yao A, Kyo S, Komuro I. Urine osmolality estimated using urine urea nitrogen, sodium and creatinine can effectively predict response to tolvaptan in decompensated heart failure patients. Circ J 2013;77:1208-13.

[9]	Costello-Boerrigter LC, Boerrigter G, Burnett JC, Jr. Pharmacology of vasopressin antagonists. Heart Fail Rev 2009;14:75-82.

[10]	Moghazi S, Jones E, Schroepple J, Arya K, McClellan W, Hennigar RA, O'Neill WC. Correlation of renal histopathology with sonographic findings. Kidney Int 2005;67:1515-20.

[11]	ACR–SPR. practice parameter for the performance of computed tomography (CT) of the abdomen and computed tomography (CT) of the pelvis. Res. 32 – 2011, Amended 2014 (Res. 39).

[12]	Toh N, Morita H, Nagase S, Taniguchi M, Miura D, Nishii N, Nakamura K, Ohe T, Kusano KF, Ito H. Atrial electrophysiological and structural remodeling in high-risk patients with Brugada syndrome: Assessment with electrophysiology and echocardiography. Heart Rhythm 2010;7:218-24.

[13]	Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-92.

[14]	Glodny B, Unterholzner V, Taferner B, Hofmann KJ, Rehder P, Strasak A, Petersen J. Normal kidney size and its influencing factors - a 64-slice MDCT study of 1.040 asymptomatic patients. BMC Urol 2009;9:19.

[15]	Buchholz NP, Abbas F, Biyabani SR, Afzal M, Javed Q, Rizvi I, Talati J. Ultrasonographic renal size in individuals without known renal disease. J Pak Med Assoc 2000;50:12-6.

[16]	Kojima K. CT of the kidney in chronic renal failure. Journal of Okayama Medical Association 2010;100:857-72.

[17]	Lang CC, Struthers AD. Targeting the renin-angiotensin-aldosterone system in heart failure. Nat Rev Cardiol 2013;10:125-34.

[18]	Nakamura K, Kusano K, Nakamura Y, Kakishita M, Ohta K, Nagase S, Yamamoto M, Miyaji K, Saito H, Morita H, Emori T, Matsubara H, Toyokuni S, Ohe T. Carvedilol decreases elevated oxidative stress in human failing myocardium. Circulation 2002;105:2867-71.

Appendix

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Figure Legends

Fig. 1. Patient selection flow diagram

Of the 159 patients registered in the Tolvaptan Registry, a total of 45 patients were excluded from this analysis because of insufficient data collection or exclusion criteria.   Data for 114 patients were analyzed in this study.

Fig. 2. Measurement of kidney size with coronal section images of multi detector-row computed tomography.

The longest longitudinal length of the kidney on each side was measured.   We defined kidney size as mean longitudinal length on the two sides.

A, Representative image of the longest longitudinal lengths of the two kidneys on the same section in a male responder.   Kidney size was defined as mean kidney length.   The patient's eGFR was low (40.8 mL/min/1.73 m^2), but his kidney size was normal (10.4 cm).

B, Representative images of the longest longitudinal lengths of the right (a) and left (b) kidneys of a male non-responder.   Kidney size was defined as mean kidney length.   The patient's eGFR was 57.2 mL/min/1.73 m^2, but his kidney was atrophic (7.2 cm).

Fig. 3. Patient enrollment

The patients (72±15 years old, 65 men) were divided into two groups: 71 patients (62%) were responders and 43 patients were non-responders.

Fig. 4. Effects of tolvaptan.

A, Changes in urine volume in responders and non-responders.　Mean urine volume was significantly increased on days 1 and 2 of tolvaptan administration in non-responders. *P<0.05 versus urine volume on day 0 in non-responders.　Mean urine volume significantly increased during the 3 days of tolvaptan administration in responders. **P<0.001 versus urine volume on day 0 in responders.　Urine volume was significantly greater in responders than in non-responders during the 3 days of treatment.　Data are mean ± standard deviation.

B, Changes in NYHA class in responders and non-responders.　Median NYHA class was significantly decreased on day 3 of tolvaptan administration in both groups. NYHA class was significantly lower in responders than in non-responders on day 3 of tolvaptan treatment. #P<0.001 versus NYHA class on day 3 in non-responders.

C, Changes in cardiothoracic ratio (CTR).　CTR in responders was significantly decreased after tolvaptan treatment, but it was not decreased in non-responders.　CTR was significantly lower in responders than in non-responders on day 3 of tolvaptan treatment. ##P<0.0001 versus CTR on day 3 in non-responders.　Data are mean ± standard deviation.