

A Diuretic Response is Associated with the Early Prognosis of Patients Undergoing Repeat Tricuspid Valve Surgery Due to Severe Tricuspid Regurgitation After Left-Sided Valvular Surgery

Ruofan Liu, Jianping Xu, Yuntao Li, Bin Li, Shen Liu, Guangyu Pan, Minghui Tong

Department of Cardiac Surgery, Heart Center, Peking University International Hospital, Beijing, China

ABSTRACT

Objective: To analyze the factors affecting the early prognosis of patients undergoing repeat tricuspid valve surgery due to severe tricuspid regurgitation after left-sided valvular surgery.

Method: We retrospectively analyzed 76 patients undergoing repeat tricuspid valve surgery due to severe tricuspid regurgitation after left-sided valvular surgery at Peking University International Hospital between October 2017 and February 2021. Patients were divided into two groups, according to preoperative weight control and whether the adjusted diuretic dose exceeded 40 mg of furosemide (or the equivalent dose). The factors affecting the early prognosis were analyzed through postoperative follow up.

Results: Thirty-five male patients (46.1%), aged 57 ± 13 years, were enrolled in the study. For the patients who received a preoperative same dose of furosemide ≥ 40 mg/day and a same dose of furosemide < 40 mg/day, the baseline data basically were the same. There were 76 patients (100%) who were followed up. Endpoint events during the follow up were as follows: Six patients (7.9%) died, two patients (2.6%) were admitted to the hospital or transferred to the intensive care unit due to cardiac insufficiency, and other conditions such as severe tricuspid regurgitation on repeat ultrasound, bilateral lower extremity edema, and inability to reduce or stop diuretics were found in five cases (6.6%). Compared with the group with the same dose of furosemide < 40 mg/day group, the ≥ 40 mg/day group had a higher incidence of endpoints (12, 27.3% vs. 1, 3.1%, $P = 0.006$).

Conclusion: In patients undergoing repeat tricuspid valve surgery due to severe tricuspid regurgitation after left-sided valvular surgery, a diuretic response was associated with surgical prognosis. Compared with the low-dose furosemide

group, the high-dose group (≥ 40 mg/) had a significantly increased incidence of early events.

INTRODUCTION

Repeat tricuspid valve surgery due to severe tricuspid regurgitation after left-sided valvular surgery, as a branch of critical cardiac surgery, has a much higher mortality and perioperative complication rate than general cardiac surgery [Writing Committee M 2021]. Many studies have analyzed its risk factors in detail [Mao 2016], but the timing of the surgery for this type of patient still is unclear. The guidelines hold that the occurrence of related symptoms and the degree of tricuspid annulus dilatation are important indicators for evaluating the surgical indications of these patients, and the main factors to be considered include right heart function and pulmonary hypertension. In our treatment of these patients, considering the preoperative cardiac dysfunction and the third-space fluid accumulation, it is necessary to use diuretics to reduce the body weight and the preloading of the patients.

In our experience, some patients need large doses of diuretic drugs before surgery to relieve their symptoms and improve surgical endurance due to their obvious symptoms. We found a correlation between diuretic response and early postoperative prognosis. Therefore, we conducted this study on this patient population and performed a statistical analysis of the occurrence of early-stage related events to bring attention to such patients and help develop more targeted treatment strategies.

MATERIALS AND METHODS

Research subjects: Retrospective cohort. From October 2017 to February 2021, patients undergoing repeat tricuspid valve surgery due to severe tricuspid regurgitation after left-sided valvular surgery at Peking University International Hospital were enrolled in the study. Forty-four patients took 40 mg/day furosemide (or equivalent dose) preoperatively due to medical needs, and all patients underwent cardiac surgery under cardiopulmonary bypass. Exclusion criteria: (1) younger than 18 years and (2) pregnant or mother to a newborn. The endpoint events were as follows: (1) death, (2) emergency admission or transfer to the intensive care unit

Received April 30, 2022; received in revised form June 10, 2022; accepted June 13, 2022.

Correspondence: Minghui Tong, Department of Cardiac Surgery, Heart Center, Peking University International Hospital, Beijing, China (e-mail: pkuibruofan@126.com).

(ICU) due to cardiac insufficiency, and (3) composite end-point events, including postoperative recurrence of severe tricuspid regurgitation, bilateral lower extremity edema, and aggravation of third-space fluid accumulation, such as abdominal effusion, causing an increase in the diuretic dosage or the inability to reduce or stop the diuretic.

Methods: The patients underwent routine cardiac color echocardiography, chest computed tomography (CT), and abdominal ultrasonography within one month before surgery. Complete blood count, liver and kidney function, preoperative coagulation, and myocardial injury examinations were performed on admission. All enrolled patients were evaluated for clinical and echocardiographic cardiac function. After 3-7 days of preoperative drug treatment, the goal of adjustment was to reduce the weight of the patient ≥ 3 kg. Patients with a dose (or equivalent dose) of furosemide exceeding 40 mg/day were defined as having a poor response to diuretics. Using the original midline sternotomy, the operator performed repeat cardiac surgery under hypothermia and cardiopulmonary bypass. According to the patient's tricuspid valve disease, the appropriate surgical method was chosen. If conditions permitted, valvuloplasty was preferred. After the cardiopulmonary bypass was stopped, the esophageal ultrasound was re-examined. If the regurgitation was more than mild, the valvuloplasty or valve replacement was reperformed under cardiopulmonary bypass, and the heart valve was repaired until the regurgitation was mild or less. All patients underwent volume management and cardiac function adjustment under the monitoring of circulatory indicators. All patients were followed up after discharge via outpatient visits and telephone calls for an average of 442 days. Patients were divided into the event-occurring group ($N = 13$) and the no-event group ($N = 63$), according to whether an end-point event occurred.

Statistical methods: SPSS 24.0 was used to analyze the data. Normally distributed measurement data are expressed as $\bar{x} \pm s$. Comparisons between the two groups were performed with Student's *t* test. Count data are expressed as number of cases and percentage and were compared between groups by the χ^2 test. Cox regression analysis was performed to quantify the relationship between each risk factor and prognosis. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of general conditions: All 76 patients (100%) were followed up in this study. According to the type of disease, 14 patients (18.4%) had isolated tricuspid regurgitation, and 62 patients (81.6%) also had left-sided valve surgery during the same period. There were 67 patients (88.2%) with two surgeries, seven patients (9.2%) with three surgeries, and two patients (2.6%) with four or more surgeries. According to the type of surgery, 12 patients (15.8%) had isolated tricuspid valve surgery, and 64 patients also had left-sided valve problems (paravalvular leak repair, valve replacement, etc.) during the same period. The average time

since the last surgery was 16.12 ± 8.23 years. The sample had 35 (46.1%) males. The average age was 57 ± 13 years. There were 60 patients (78.9%) with preoperative atrial fibrillation and three patients (3.9%) with preoperative administration of vasoactive drugs. The preoperative cardiothoracic ratio was 0.66 ± 0.12 , and the preoperative ultrasound ejection fraction (EF) was $61.95 \pm 8.47\%$. The operative duration was 401.84 ± 176.17 min. Seventy-two patients underwent tricuspid annuloplasty (55 annuloplasty ring implantation and 17 suture annuloplasty), and four underwent tricuspid valve replacement, all of which were implanted with mechanical valves. The postoperative central venous pressure (CVP) was 6.96 ± 3.84 mmHg, the drainage volume was 407.21 ± 221.05 ml at 24 hours after surgery, average ventilator duration was 46.13 ± 70.39 hours, and ICU stay was 4.09 ± 4.31 days. The amount of dehydration was 2700.16 ± 2141.19 ml during the ICU stay. During the follow up, six patients (7.9%) died, two patients (2.6%) were admitted to the hospital or transferred to the ICU due to cardiac insufficiency, and five patients (6.6%) experienced other conditions such as abnormal repeat ultrasound, bilateral lower limb edema, and inability to reduce or stop the diuretic. As shown in Table 1, the baseline data of patients who received an equivalent dose of furosemide ≥ 40 mg/day before surgery and those who used an equivalent dose of furosemide < 40 mg/day were basically consistent, including sex; age; preoperative weight loss; incidence of atrial fibrillation; laboratory indicators such as brain natriuretic peptide (BNP), C-reactive protein, creatinine, and bilirubin; and ultrasound indicators such as preoperative left ventricular size and EF value. (Table 1) In the furosemide ≥ 40 mg/day group, the preoperative hemoglobin level was significantly lower than that in the low-dose group (104 ± 28 g/L vs. 122 ± 23 g/L, $p = 0.006$), and the proportion of patients with preoperative clinical cardiac function class III-IV also was significantly higher than that in the low-dose group (25, 56.8% vs. 9, 28.1%, $P = 0.019$, Table 1).

Comparison of postoperative follow-up results: A comprehensive analysis of the intraoperative and postoperative conditions showed that the high-dose furosemide group had higher intraoperative ultrafiltration volume (3535.71 ± 2676.62 ml vs. 2203.23 ± 1218.88 ml, $P = 0.012$), higher immediate postoperative CVP after postoperative adjustment (7.75 ± 4.37 vs. 5.84 ± 2.61 , $P = 0.033$), longer postoperative ventilator application was increased (61.75 ± 88.61 vs. 24.66 ± 16.51 , $P = 0.022$), and longer hospital stay in the ICU (5.05 ± 5.43 vs. 2.78 ± 1.01 , $P = 0.023$). In addition, the incidence of endpoint events in the high-dose group was significantly higher than that in the low-dose group (12, 27.3% vs. 1, 3.1%, $P = 0.006$).

Multivariate analysis of endpoint events: When we included age, sex, preoperative cardiac function evaluated by echocardiography, preoperative clinical cardiac function, preoperative hemoglobin level, and preoperative use of high-dose diuretic in the multivariate analysis, preoperative use of high-dose diuretic was the only independent predictor of adverse events. (Table 2)

Survival curve: The survival curve analysis showed that the incidence of early events was significantly increased in the high-dose group. (Figure 1)

Table 1. Comparison of general information of the two groups of patients

Factor	Data (76)	Furosemide \geq 40 mg/day (44)	Furosemide <40 mg/day (32)	P-value
Age (years)	57 \pm 13	56 \pm 14	58 \pm 13	0.569
Sex (male, %)	35 (46.1)	18 (56.3)	17 (38.6)	0.164
EuroSCORE II (%)	11.18 \pm 10.43	12.22 \pm 11.02	9.76 \pm 9.53	0.314
Preoperative weight loss (kg)	1.84 \pm 2.25	2.00 \pm 2.33	1.09 \pm 1.72	0.189
Hemoglobin (g/L)	112 \pm 27	104 \pm 28	122 \pm 23	0.006
Creatinine	80.58 \pm 20.23	80.48 \pm 20.91	80.72 \pm 26.07	0.967
Urea nitrogen	8.63 \pm 3.73	8.9 \pm 3.9	8.28 \pm 3.48	0.481
Transaminase	20.5 \pm 16.34	20.07 \pm 15.36	21.09 \pm 17.84	0.789
BNP	320.35 \pm 302.8	301.6 \pm 276.3	346.9 \pm 339.8	0.527
Left ventricular size (ml)	48.4 \pm 8.05	47.7 \pm 7.26	49.4 \pm 9	0.355
EF value	61.95 \pm 8.47	60.77 \pm 8.77	63.57 \pm 7.87	0.156
Preoperative albumin	39.68 \pm 3.8	39.45 \pm 4.1	39.99 \pm 3.4	0.550
Preoperative cardiothoracic ratio	0.66 \pm 0.12	0.68 \pm 0.13	0.64 \pm 0.11	0.214
Preoperative left atrial size (ml)	73 \pm 23	70 \pm 22	78 \pm 25	0.176
Patients with low cardiac output symptom within 3 months before surgery	8 (10.5)	2 (6.3)	6 (13.6)	0.455
Combined diabetes	6 (7.9)	1 (3.1)	5 (11.4)	0.392
Atrial fibrillation	60 (78.9)	36 (81.8)	24 (75)	0.572
Preoperative cardiac function class III-IV	34 (44.7)	25 (56.8)	9 (28.1)	0.019
EF value>50%	71 (93.4)	41 (93.2)	30 (93.8)	1.000
Isolated tricuspid valve surgery	12 (15.8)	8 (18.2)	4 (12.5)	0.545

LVEF, left ventricular ejection fraction

Table 2. Comparison of outcomes between high-dose and low-dose groups

Factor	Total (N = 76)	Furosemide \geq 40 mg/day (N = 44)	Furosemide <40 mg/day (N = 32)	P-value
Operation duration (min)	401.84 \pm 176.17	436.45 \pm 218.93	352.71 \pm 60.02	0.042
Transfer time (min)	206.11 \pm 109.76	224.57 \pm 134.6	181.1 \pm 55	0.095
Blocking time (min)	145.26 \pm 106.34	139.55 \pm 84.18	153 \pm 131.7	0.597
Intraoperative ultrafiltration volume (ml)	2969.86 \pm 2266.83	3535.71 \pm 2676.62	2203.23 \pm 1218.88	0.012
Immediate postoperative CVP (mmHg)	6.96 \pm 3.84	7.75 \pm 4.37	5.84 \pm 2.61	0.033
24-hour postoperative drainage (ml)	407.21 \pm 221.05	412.07 \pm 217.63	400.53 \pm 228.99	0.824
Ventilator duration (h)	46.13 \pm 70.39	61.75 \pm 88.61	24.66 \pm 16.51	0.022
Day of hospitalization in the ICU (d)	4.09 \pm 4.31	5.05 \pm 5.43	2.78 \pm 1.01	0.023
Volume in the ICU (ml)	-2700.16 \pm 2141.19	-2849.12 \pm 2405.41	-2495.34 \pm 1729.59	0.481
Outcome	13 (17.1)	12 (27.3)	1 (3.1)	0.006

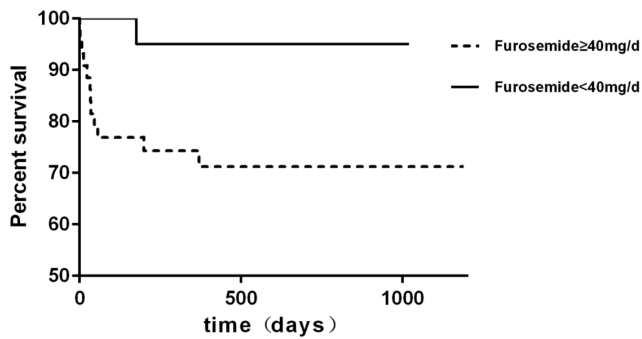


Figure 1. Survival curve

DISCUSSION

Patients with severe tricuspid regurgitation after left-sided valvular surgery underwent repeat tricuspid valve surgery, and the perioperative mortality and the incidence of cardiovascular events were much higher than those of patients undergoing general cardiac surgery [Writing Committee M 2021]. Previous studies have searched for risk factors for perioperative events of reoperation [LaPar 2018], and there is no clear significant difference in the prognosis between repeat tricuspid valve surgery and combined left-sided valve surgery at the same time [Writing Committee M 2021]. This study was the first to observe a correlation between poor diuretic response and early prognosis in patients with severe tricuspid regurgitation after left-sided valvular surgery.

The phenomenon of diuretic resistance has been widely recognized for decades, but a clear definition is lacking [Voors 2014]. In our study, patients with severe tricuspid regurgitation after left-sided valvular surgery often were associated with third-space fluid accumulation. Diuretics often were used to reduce preload and improve cardiac function before surgery. We controlled the diuretic intake according to the patient's condition and evaluated the effectiveness of the preoperative treatment based on the weight loss. In this sequential treatment process, patients who received an equivalent dose of furosemide of ≥ 40 mg/day were defined as having poor diuretic response (high-dose group). The incidence of early related events was higher in these patients. The above may be a more practical way to assess the timing of surgery.

According to the latest guidelines, the two most important factors in the long-term prognosis of these patients are right ventricular failure and irreversible pulmonary hypertension [Writing Committee M 2021]. However, considering the risk of reoperation, the timing of surgery still is inconclusive. The status of right heart function is the main factor influencing the prognosis of these patients [Writing Committee M 2021], but unlike in the left heart system, there is no clear evaluation standard for right heart function [Kwon 2006]. Among the patients we included, the results of color Doppler cardiac ultrasound suggested that the left heart function was normal, which increased the difficulty of our preoperative evaluation.

There are many previous studies on the correlation between diuretic response and the early prognosis of patients

Table 3.

Predictor	P	HR	95% CI
Age (years)	0.480	1.019	0.967-1.074
Sex (male)	0.281	0.520	0.159-1.704
EF $\geq 50\%$	0.972	0.961	0.107-8.615
Clinical cardiac function class III-IV	0.801	1.175	0.335-4.124
Preoperative hemoglobin	0.689	0.995	0.974-1.018
Furosemide ≥ 40 mg/day	0.026	9.977	1.118-89.046

with acute heart failure. In contrast to previous studies [ter Maaten 2015], we found that patients with severe tricuspid regurgitation after left-sided valvular surgery often had a chronic progressive process. One drawback of previous studies is the lack of comparison. We used the observation of the dose of diuretic during the adjustment process (whether it exceeded 40 mg) as the standard for our evaluation.

The baseline data of the two groups basically were consistent. Under unified postoperative management conditions, although there was no significant difference in postoperative related indicators, the high-dose group had a higher incidence of endpoint events (12, 27.3% vs. 1, 3.1%, $P = 0.006$). This suggests that the patients' right heart function was severely impaired.

Previous studies have suggested that diuretic resistance is associated with renal dysfunction, diabetes, atherosclerotic diseases, more severe heart failure, and rapid in-hospital worsening heart failure [Voors 2014]. It also predicts the risk of mortality and rehospitalization due to heart failure. Intuitively, patients with poor diuretic response have worse renal function, but renal insufficiency only partially explains the situation of diuretic resistance [Valente 2014; Testani 2014]. There was no significant difference in preoperative creatinine level between the patients with severe tricuspid regurgitation after left-sided valvular surgery. Although one study did not assess renal atherosclerosis, it performed coronary artery assessment on patients over 50 years of age before surgery, and the impact of coronary atherosclerosis confidently was excluded. In the assessment of cardiac function, there was no significant difference between the status of left ventricular function and the patient's symptoms [Voors 2014].

Current studies suggest that poor diuretic response occurs in patients with cardiac insufficiency, mainly for the following reasons: 1) The acidic internal environment of patients mitigates the effect of diuretics. Patients with heart failure have higher levels of circulating organic acids (such as urea nitrogen), which can hinder the function of diuretics in functional areas, leading to diuretic resistance. 2) The activation of the renin-angiotensin-aldosterone (RAAS) system and the sympathetic nervous system can cause urea to undergo reabsorption in the distal renal tubules increasing the water and sodium retention in the proximal tubules, and the resulting concentration gradient can slow the flow of urine in the distal tubules and increase its reabsorption, which weakens the function of diuretics. 3) The steady-state response leads to

diuretic resistance. At the beginning of treatment with diuretics, natriuretic drugs can cause negative sodium balance. The lessening of extracellular fluid triggers a response to maintain homeostasis, which response increases the retention of sodium in the renal tubules to establish a new homeostasis. Patients with heart failure have an increase in secondary aldosterone, which can rapidly induce the reabsorption of a large amount of sodium and lead to diuretic resistance. In addition, distal tubule hypertrophy raises sodium retention [Kennelly 2021; Kristjansdottir 2020].

We believe that in patients with severe tricuspid regurgitation after left-sided valve surgery, these factors coexist and affect each other, causing and aggravating diuretic resistance. First, the preoperative urea nitrogen level in these patients was relatively high (8.63 ± 3.73 mmol/L). Second, the increase in third-space fluid and the decrease in renal blood flow could cause the activation of the RAAS system and the sympathetic nervous system, which are pathophysiologic changes that precede clinical symptoms. Effective identification of these pathological conditions, correcting the state of tricuspid regurgitation, and improving right ventricular function before the disease progresses to irreversible decompensation of right ventricular function may be an effective means to improve the clinical prognosis of these patients.

When there is a severe tricuspid regurgitation after left-sided valve surgery and the surgical evaluation leads to the consideration of repeat tricuspid valve surgery, the patient needs a high dose of diuretic to effectively control their body weight. In such situations, we need to be aware that correction of the tricuspid regurgitation anatomy may not reverse the pathological changes in such patients, which may cause the postoperative diuretic dependence to persist or even worsen, which may aggravate the risk of postoperative adverse events. In this regard, whether active surgical intervention is beneficial may require further in-depth study.

LIMITATIONS

This was a retrospective analysis of patients with poor diuretic responsiveness. It did not monitor urinary sodium concentration and the assessment of renal atherosclerosis are lacking. The quantitative analysis of the diuretic response requires more rigorous, prospective case studies to further clarify the impact of diuretic response on the prognosis of these patients undergoing repeat valve surgery.

CONCLUSION

For patients undergoing severe tricuspid regurgitation after left-sided tricuspid surgery, diuretic response was

associated with the prognosis of the surgery. The incidence of early events increased significantly in the high-dose furosemide group (≥ 40 mg/day).

ACKNOWLEDGEMENT

Funding: This study was supported by Project supported by Peking University International Hospital Research Grant (No. YN2021QX01).

REFERENCES

- Kennelly P, Sapkota R, Azhar M, Cheema FH, Conway C, Hameed A. 2021. Diuretic therapy in congestive heart failure. *Acta Cardiol.* 1-8.
- Kristjansdottir I, Thorvaldsen T, Lund LH. 2020. Congestion and Diuretic Resistance in Acute or Worsening Heart Failure. *Card Fail Rev.* 6:e25.
- Kwon DA, Park JS, Chang HJ, et al. 2006. Prediction of outcome in patients undergoing surgery for severe tricuspid regurgitation following mitral valve surgery and role of tricuspid annular systolic velocity. *Am J Cardiol.* 98:659-61.
- LaPar DJ, Likosky DS, Zhang M, et al. 2018. Development of a Risk Prediction Model and Clinical Risk Score for Isolated Tricuspid Valve Surgery. *Ann Thorac Surg.* 106:129-136.
- Mao B, Sun L, Zhang J, Zhou M, Zhang F. 2016. Perioperative factors associated with short- and long-term outcomes after tricuspid valve replacement. *Interact Cardiovasc Thorac Surg.* 23:845-850.
- ter Maaten JM, Dunning AM, Valente MA, et al. 2015. Diuretic response in acute heart failure—an analysis from ASCEND-HF. *Am Heart J.* 170:313-21.
- Testani JM, Brisco MA, Turner JM, et al. 2014. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail.* 7:261-70.
- Valente MA, Voors AA, Damman K, et al. 2014. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J.* 35:1284-93.
- Voors AA, Davison BA, Teerlink JR, et al. 2014. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. *Eur J Heart Fail.* 16:1230-40.
- Writing Committee M, Otto CM, Nishimura RA, et al. 2021. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 77:450-500.