Peak Lag Between Plasma Vasopressin and Urine Aquaporin-2 Following Cardiac Surgery

Departement of Surgery 1
Faculty of Medicine, University of Toyama

Shigeki Yokoyama

ABSTRACT

Background:
Tolvaptan, a vasopressin type-2 receptor antagonist, is recently utilized to ameliorate fluid retention following cardiac surgery. However, the optimal timing of tolvaptan administration remains unknown.

Methods:
I prospectively included patients who underwent cardiac surgery between 2016 and 2020. I measured trends of free water reabsorption mediators including plasma arginine vasopressin and urine aquaporin-2 perioperatively.

Results:
Consecutive 20 patients (68 [60, 75] years old, 18 men) were included. Urine volume decreased gradually after the initial 3 hours following cardiac surgery. Following cardiac surgery, plasma arginine vasopressin level increased significantly with a peak at postoperative 6 hours, whereas urine aquaporin-2 level later with a delayed peak at postoperative 12 hours.

Conclusions:
Plasma arginine level increased following cardiac surgery, whereas urine aquaporin-2, which is a marker of responder to tolvaptan, increased later with a delayed peak. Tolvaptan administration immediately after cardiac surgery might not be effective given the transient stunning of kidney collecting duct.

Keywords: heart failure; hemodynamics; diuretics, Tolvaptan

BACKGROUND

Despite the improvement in perioperative clinical management and surgical technique, fluid overload is one of the critical issues associating with mortality and morbidity following cardiac surgery.[1] Loop diuretic is a conventional therapeutic tool to treat post-operative fluid overload,[2] but is associated with poor clinical outcomes owing to the stimulations of sympathetic nerve activity and renin-angiotensin-aldosterone system, progression of hyponatremia, hypotension, and tachycardia.[1]

Tolvaptan, a vasopressin type-2 receptor antagonist, is a recently-introduced novel diuretic that suppresses reabsorption of free water in the kidney collecting duct and increases urine output, maintaining hemodynamics and renal function and improving quality of life in various clinical situations accompanying fluid overload.[2]

Recent studies demonstrated clinical implications to administer tolvaptan peri-operatively in patients receiving cardiac surgery in improving postoperative clinical outcomes by ameliorating fluid overload.[3-8] However, the optimal timing to administer tolvaptan remains uncertain. I speculated that inflammation of renal function after cardiac surgery may have delayed activation of urinary aquaporin-2, a marker of responsiveness to tolvaptan.[9,10]

Based on this hypothesis, I investigated trends of plasma arginine vasopressin (AVP) and urine aquaporin-2 (AQP2), both of which are dominant mediators of free water reabsorption in the kidney,[9] following cardiac surgery in order to discuss the optimal timing of tolvaptan administration.[10] This doctoral dissertation is based on a paper. [10]

METHODS

Patient selection:

Consecutive patients who underwent scheduled cardiac surgery at our institute (Toyama University hospital) between September 2016 and March 2020 were prospectively included in this study. Patients dependent on hemodiafiltration and those with estimated glomerular filtration ratio <30 mL/min/1.73m^2 were excluded. The study protocol was approved by the local ethical committee. All participants gave written informed consent before the enrollment.

Operative technique and perioperative management:

All patients underwent cardiac surgery via a mid-sternotomy incision. The cardiopulmonary bypass system was established by the standard technique and performed at a moderate hypothermia (30-32 degrees). Myocardial protection during the operation included intermittent antegrade cold blood cardioplesia. The off-pump coronary artery bypass grafting surgery was performed at normothermia. Postoperative management was performed according to the standard cardiac surgery postoperative management. Diuretics including furosemide were not administered in all patients.

Data collection:

Patients' baseline characteristics including demographic data within 24 hours before the cardiac surgery and operation data were collected. Plasma AVP and urine AQP2 levels were measured within 24 hours before the cardiac surgery as baseline variables.

Following the cardiac surgery, urine volumes were measured every one hour during the initial 24 hours. Plasma AVP and urine AQP2 levels were measured at postoperative 6 hours, 12 hours, and 1 week.

Statistical analyses:

Continuous variables were stated as median and interquartile. Categorical variables were stated as number and percentage. Trends were assessed by using the Friedman test and ad-hoc Wilcoxon signed-rank test versus baseline values. The response to tolvaptan was predicted by urine AQP2 / plasma AVP, which indicates residual ability of kidney collecting duct to increase AQP2 by responding to the stimulation of AVP.[9] Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Armonk, IL, USA). Two-sided p-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics:

Twenty patients (68 [60, 75] years old, 18 men) were included. Of them, 8 underwent off-pump coronary artery bypass grafting, 9 underwent valve surgery, and 3 underwent valve surgery and coronary artery bypass grafting. Baseline characteristics are summarized in Table 1.

Trends of urine volume:

Trends of urine volume during the initial 24 hours following cardiac surgeries are summarized in Figure 1. The urine volume per hour gradually decreased with a peak at postoperative 2 hours ($p < 0.001$).

Perioperative trends of urine volume mediators:

Following cardiac surgeries, plasma AVP level increased significantly with a peak value at postoperative 6 hours ($p < 0.05$; Figure 2A). Urine AQP2 level increased gradually following cardiac surgeries with a peak value at postoperative 12 hours ($p < 0.05$; Figure 2B).

As a result, a plasma AVP peak is located at 6 hours (a red arrow in Figure 1), followed by a urine APQ2 peak at 12 hours (a blue arrow in Figure 1), as well as gradual decreases in urine volume after the initial 6 hours.

Perioperative trend of estimated responses to tolvaptan:

At baseline, median urine AQP2 / plasma AVP, which is an estimated response to tolvaptan indicating preserved function of kidney collecting duct, was 2.4

(1.3, 4.5) $\times 10^3$ (Figure 3). All patients had values above 0.5 $\times 10^3$, which was a cutoff of responder proposed in the previous study.[9] Following the surgery, the value dropped transiently at postoperative 6 hours down to 0.6 (0.3, 1.2) $\times 10^3$ ($p < 0.05$) and recovered at 12 hours.

Urine AQP2 / plasma AVP levels at postoperative 6 hours tended to be lower in patients with cardiopulmonary bypass (N = 12) than those without (N = 8) (0.5 [0.3, 0.9] versus 1.1 [0.4, 1.3] $\times 10^3$, $p = 0.34$).

DISCUSSION

In this prospective study, I investigated the trends of free water reabsorption mediators including plasma AVP and urine AQP2 following cardiac surgery. A peak of plasma AVP was observed at 6 hours whereas that of urine AQP2 was observed at 12 hours when urine volume per hour was consistently lower. Urine AQP2 level relative to plasma AVP was preserved in all patients at baseline ($>0.5 \times 10^3$), decreasing transiently at 6 hours and recovering at 12 hours.

Fluid retention following cardiac surgery:

Fluid retention is often encountered following cardiac surgery and is associated with mortality and morbidity.[1] Hemodilution due to cardiopulmonary bypass stimulates osmotic pathway and increases plasma AVP level.[11] Reperfusion injures the myocardium and provokes transient heart failure, which stimulates non-osmotic pathway and also increases plasma AVP level.[12] Increased plasma AVP stimulates vasopressin type-2 receptors located on the kidney collecting duct and facilitates reabsorption of free water via activating AQP2 system.[13] Perioperative inflammation increases vascular permeability and worsens interstitial edema.[11] Given these mechanisms, tolvaptan, a vasopressin type-2 receptor antagonist, receives great concern to correct postoperative fluid retention.

Perioperative concomitant tolvaptan therapy:

Several studies demonstrated that tolvaptan concomitant therapy was associated with higher urine output, earlier body weight recovery, and shorter hospitalization length compared with a conventional loop diuretics therapy in patients

receiving cardiac surgery.[3-8] Reno-protective effect of tolvaptan therapy was also observed in some of them.[4, 8] Tolvaptan seems to be administered immediately following the cardiac surgery in most of the studies. However, theoretically and clinically optimal timing of tolvaptan therapy has not been discussed.

Optimal timing of tolvaptan administration:

In general, urine AQP2 level should have a positive correlation with plasma AVP level when kidney collecting duct function is preserved.[9] In this study, I observed a "time lag" between the peak of plasma AVP (at postoperative 6 hours) and the peak of urine AQP2 (at postoperative 12 hours). Consistently, urine AQP2 level relative to plasma AVP, which indicates residual function of kidney collecting duct and a predictor of response to tolvaptan, decreased transiently at 6 hours and normalized at 12 hours.

Given that tolvaptan increases urine volume by suppressing the activity of AQP2 system,[13] optimal timing of tolvaptan administration might be relatively later instead of the postoperative immediate phase that most of the studies adopted. Such a knowledge should be useful particularly several years later, when intra-venous tolvaptan will be clinically available.

The detailed mechanism that explains the time lag remains unknown, but the inflammatory injury of kidney interstitial tissue by the invasion of cardiac surgery including cardiopulmonary bypass might transiently suppress the activity of kidney collecting duct at the postoperative immediate phase.[14]

Another concern is optimal patient selection. Previous studies demonstrated that a decrease in urine osmolality following the administration of tolvaptan and a shorter cardiopulmonary bypass time were associated with good response to tolvaptan

among those receiving cardiac surgery.[3, 4, 7, 8] In my study, all patients satisfied urine AQP2/plasma AVP >0.5 $\times 10^3$ at baseline, which is another cutoff of responders to tolvaptan.[9]

Limitations:

The sample size is small. I observed a time lag between plasma AVP and urine AQP2 but the mechanism to explain this phenomenon remains within speculation. I did not analyze the response to tolvaptan, which should be assessed in the next prospective randomized control trial comparing between early tolvaptan therapy (at 6 postoperative hours) and late tolvaptan therapy (at postoperative 12 hours).

Conclusion:

Plasma arginine vasopressin level increased following cardiac surgery, whereas urine aquaporin-2, which is a marker of the responder to tolvaptan, increased later with a delayed peak. Tolvaptan administration immediately after cardiac surgery might not be effective given transient stunning of the kidney collecting duct.

REFERENCES

1. Stein A, de Souza LV, Belettini CR, Menegazzo WR, Viegas JR, Costa Pereira EM, Eick R, Araujo L, Consolim-Colombo F, Irigoyen MC. Fluid Overload and Changes in Serum Creatinine After Cardiac Surgery: Predictors of Mortality and Longer Intensive Care Stay. A Prospective Cohort Study. Crit Care. 2012;16(3):R99.
2. Imamura T, Kinugawa K. Update of Acute and Long-Term Tolvaptan Therapy. J Cardiol. 2019;73(2):102-7.
3. Ito H, Mizumoto T, Tempaku H, Fujinaga K, Sawada Y, Shimpo H. Efficacy of Tolvaptan on Fluid Management After Cardiovascular Surgery Using Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 2016;30(6):1471-8.
4. Yamada M, Nishi H, Sekiya N, Horikawa K, Takahashi T, Sawa Y. The Efficacy of Tolvaptan in the Perioperative Management of Chronic Kidney Disease Patients Undergoing Open-Heart Surgery. Surg Today. 2017;47(4):498-505.
5. Hagiwara S, Nishida N, Chishina H, Ida H, Sakurai T, Komeda Y, Kitano M, Kudo M. Cases with Refractory Ascites and a Delayed Response to Tolvaptan. Intern Med. 2016;55(22):3273-7.
6. Nishi H, Toda K, Miyagawa S, Yoshikawa Y, Fukushima S, Kawamura M, Yoshioka D, Saito T, Ueno T, Kuratani T, Sawa Y. Effects of Tolvaptan in the Early Postoperative Stage After Heart Valve Surgery: Results of the STAR (Study of Tolvaptan for Fluid Retention After Valve Surgery) Trial. Surg Today. 2015;45(12):1542-51.
7. Kishimoto Y, Nakamura Y, Harada S, Onohara T, Kishimoto S, Kurashiki T, Fujiwara Y, Nishimura M. Can Tolvaptan Protect Renal Function in the Early Postoperative

Period of Cardiac Surgery?- Results of a Single-Center Randomized Controlled Study. Circ J. 2018;82(4):999-1007.

8. Matsuyama K, Koizumi N, Nishibe T, Iwasaki T, Iwahasi T, Toguchi K, Takahashi S, Iwahori A, Maruno K, Ogino H. Effects of Short-Term Administration of Tolvaptan After Open Heart Surgery. Int J Cardiol. 2016;220:192-5.
9. Imamura T, Kinugawa K, Fujino T, Inaba T, Maki H, Hatano M, Yao A, Komuro I. Increased Urine Aquaporin-2 Relative to Plasma Arginine Vasopressin Is a Novel Marker of Response to Tolvaptan in Patients With Decompensated Heart Failure.Circ J. 2014;78(9):2240-9.
10. Yokoyama S, Imamura T, Yamashita S, Doi T, Fukahara K, Yoshimura N, Kinugawa K. Peak Lag Between Plasma Vasopressin and Urine Aquaporin-2 Following Cardiac Surgery. Int Heart J. 2021 Sep 30;62(5):1057-1061.
11. Jochberger S, Mayr VD, Luckner G, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Friesenecker B, Mayr AJ, Dunser MW. Serum Vasopressin Concentrations in Critically Ill Patients. Crit Care Med. 2006;34(2):293-9.
12. Kaul TK, Swaminathan R, Chatrath RR, Watson DA. Vasoactive Pressure Hormones During and After Cardiopulmonary Bypass. The International Journal of Artificial Organs. 1990;13(5):293-9.
13. Imamura T, Kinugawa K. Urine Aquaporin-2: A Promising Marker of Response to the Arginine Vasopressin Type-2 Antagonist, Tolvaptan in Patients with Congestive Heart Failure. Int J Mol Sci. 2016;17(1).
14. Kumar AB, Suneja M. Cardiopulmonary Bypass-Associated Acute Kidney Injury. Anesthesiology. 2011;114(4):964-70.

FIGURE LEGENDS

Table.1

Baseline characteristics

Continuous variables were expressed as median and interquartile and categorical variables were expressed as number and percentage.

eGFR, estimated glomerular filtration ratio.

Fig. 1

Trend in urine volume during 24 hours following cardiac surgeries

AVP, arginine vasopressin; U-AQP, urine aquaporin.

*p <0.05 by Friedman test.

Fig. 2

Perioperative trends in plasma arginine vasopressin (A) , urine aquaporin-2 (B) , and urine Osmolality.

*p <0.05 by Friedman test. †p <0.05 by post-hoc Mann-Whitney U test versus preoperative value.

Fig. 3

Perioperative trends in urine aquaporin-2 / plasmas arginine vasopressin.

The value dropped transiently at postoperative 6 hours and recovered up to the preoperative levels at 12 hours.

*p <0.05 by Friedman test. †p <0.05 by post-hoc Mann-Whitney U test versus preoperative value.

TABLE

Table1. Baseline characteristics

Demographics	
Age, years	68 (60, 75)
Men	18 (90%)
Body weight, kg	64.4 (58.0, 79.5)
Ischemic heart disease	12 (60%)
Diabetes mellitus	6 (30%)
Atrial fibrillation	5 (25%)
Operation type	
Off-pump coronary artery bypass grafting	8 (40%)
Valve surgery	9 (45%)
Valve surgery and coronary artery bypass grafting	3 (15%)
Operation time, min	193 (179, 220)
Laboratory and echocardiography	
eGFR, mL/min/1.73m^2	67.6 (58.8, 75.5)
Plasma arginine vasopressin, pg/mL	1.7 (1.2, 3.5)
Urine aquaporin-2, ng/mL	6.4 (2.1, 9.9)
Plasma NTpro-B-type natriuretic peptide, pg/mL	483 (157, 1077)
Left ventricular ejection fraction, %	65 (47, 70)

FIGURE

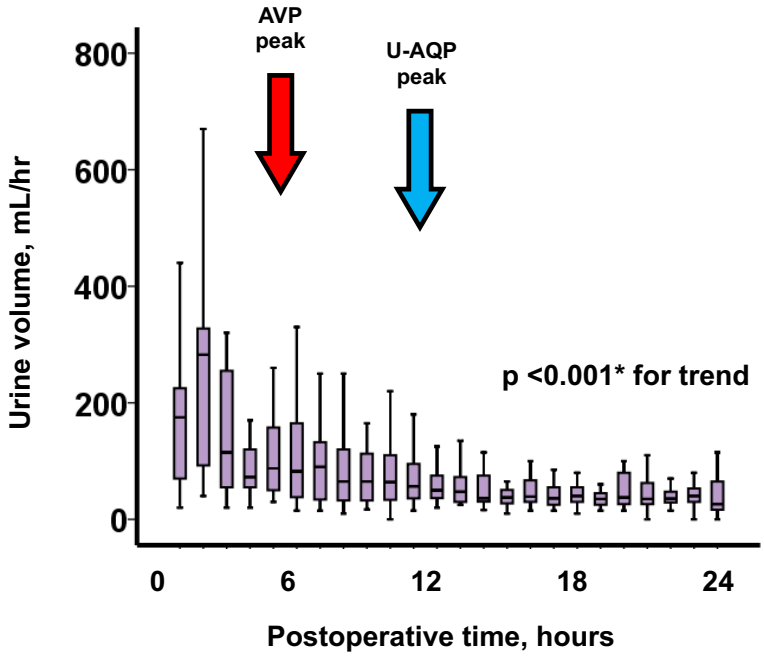

Figure 1

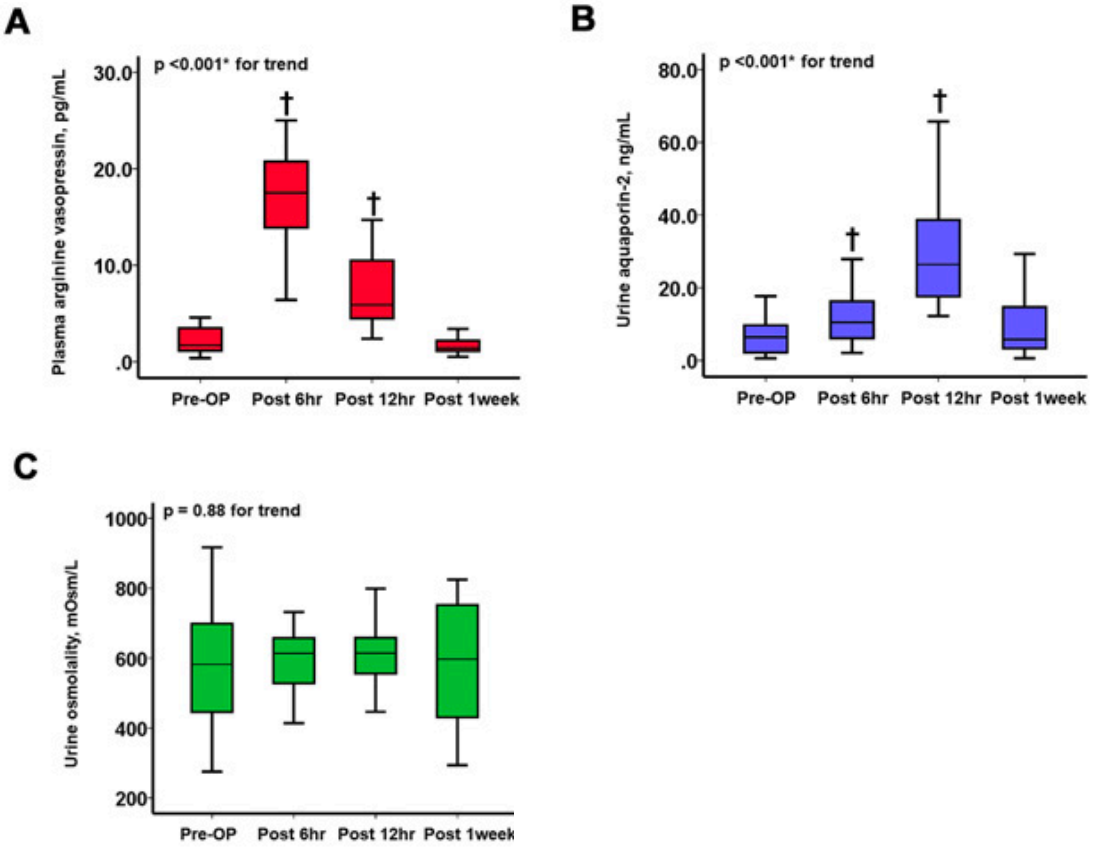
A
p <0.001* for trend
Plasma arginine vasopressin, pg/mL
30.0
20.0
10.0
.0
†
†
Pre-OP
Post 6hr
Post 12hr
Post 1week
B
p <0.001* for trend
Urine aquaporin-2, ng/mL
80.0
60.0
40.0
20.0
.0
†
†
Pre-OP
Post 6hr
Post 12hr
Post 1week
C
p = 0.88 for trend
Urine osmolality, mOsm/L
1000
800
600
400
200
Pre-OP
Post 6hr
Post 12hr
Post 1week

Figure 2

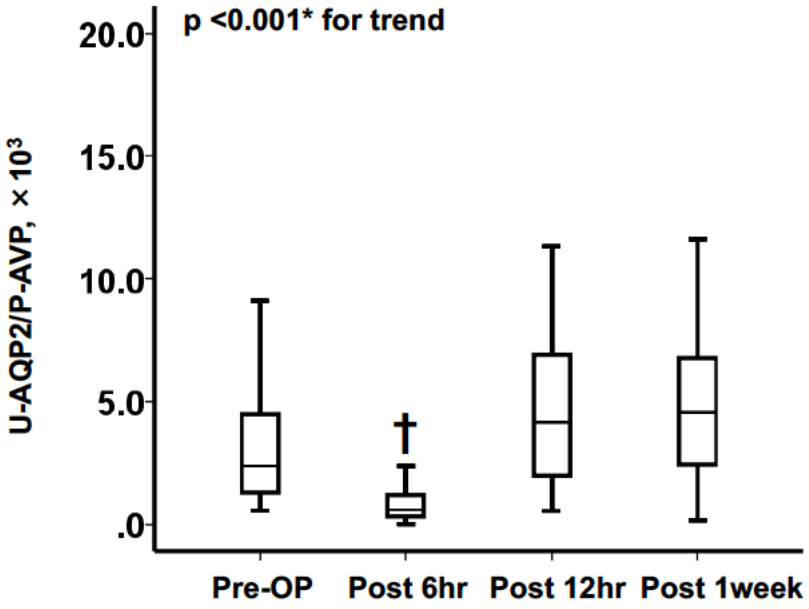
p <0.001* for trend
20.0
15.0
10.0
5.0
.0
U-AQP2/P-AVP, × 10³
†
Pre-OP
Post 6hr
Post 12hr
Post 1week

Figure 3