Perfusion parameters during cardiopulmonary bypass as a predictor of acute kidney injury after aortic valve replacement

Yeiwon Lee[1], Sue Hyun Kim[1], Ho Young Hwang[2], Suk Ho Sohn[2], Jae Woong Choi[2], Kyung Hwan Kim[2]

Departments of [1]Critical Care and [2]Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Background: Acute kidney injury (AKI) is a major complication after cardiac surgery and significantly affects postoperative mortality and morbidity. This study was conducted to evaluate the association between target pump flow to achieve adequate oxygen delivery (DO_2) and postoperative renal function after aortic valve replacement.

Methods: From January 2017 to May 2020, 281 patients (male:female, 160:121; mean age, 68±11 years) who underwent aortic valve replacement were retrospectively reviewed. Target pump flow was calculated based on DO_2 level of 280 mL/min/m². The primary endpoint was postoperative renal dysfunction, defined as the ratio of postoperative peak creatinine level to preoperative value. The ratio of the lowest actual pump flow to the ideal target pump flow, other hemodynamic variables related with cardiopulmonary bypass, intraoperative transfusion, and preoperative characteristics were analyzed to identify factors associated with the primary endpoint using a multivariable linear regression model.

Results: Preoperative and peak postoperative creatinine levels were 0.94±0.33 mg/dl and 1.15±0.56 mg/dl, respectively (ratio, 1.22±0.33). The ideal target pump flow was 4.70±0.59 L/min, whereas the lowest actual pump flow was 3.77±0.47 L/min (ratio, 0.81±0.13). The multivariable model showed that the ratio of the lowest pump flow to target pump flow (β±standard error, −0.405±0.162, P=0.013), as well as sex, stroke history, emergency operation, and transfusion of red blood cells were associated with the primary endpoint.

Conclusions: Low actual nadir pump flow compared to the ideal target pump flow based on DO_2 is associated with the risk of AKI after aortic valve replacement.

Key Words: acute kidney injury; aortic valve replacement; oxygen delivery

INTRODUCTION

Acute kidney injury (AKI) is a common postoperative complication that occurs in 20% to 40% of cardiac surgical patients [1-3]. Postoperative AKI is associated with mortality after surgery, which increases up to 50% when renal replacement therapy is required [4]. In addition, even small decreases in glomerular filtration rates might be associated with increased postoperative mortality [5]. Previous studies demonstrated various risk factors associated with occurrence of AKI after cardiac surgery [3,6-8]. These include age, diabetes mellitus, pre-existing renal dysfunction, prolonged cardiopulmonary bypass (CPB) time, and use of adrenergic med-

Lee Y, et al.   Effect of DO$_2$ during CPB after AVR

ACC

ications [3,6-8].

In addition to well-known risk factors, recent studies [9-11] have demonstrated that nadir oxygen delivery (DO$_2$) during CPB is the best predictor of AKI after cardiac surgery. These observations have led to the concept of goal-directed perfusion, which is intended to maintain the DO$_2$ level above the critical value during CPB. CPB flow is one of the modifiable risk factors for AKI and has conventionally been largely based on monitoring of a formula based on the cardiac index multiplied by the body surface area of the patient. However, pump flow based solely on a cardiac index does not ensure satisfactory DO$_2$ to the tissues, which can lead to metabolic acidosis, hyperlactatemia, and end-organ ischemia. However, high-level evidence of the association of goal-directed perfusion strategy and postoperative AKI remains lacking. Therefore, this study was conducted to evaluate the association between perfusion parameters during CPB and postoperative renal dysfunction after aortic valve replacement (AVR).

Table 1. Characteristics of the study patients

Variable	Total (n = 281)
Age (yr)	68.0 ± 11.5
Male	160 (57)
Body surface area (m²)	1.65 ± 0.18
Overweight (BMI > 25 kg/m²)	110 (39.1)
Risk factor	
Smoking	79 (28.1)
Hypertension	152 (54.1)
Diabetes mellitus	79 (28.1)
Dyslipidemia	116 (41.3)
History of stroke	25 (8.9)
Chronic kidney disease (GFR < 60 ml/min)	47 (16.7)
Chronic obstructive pulmonary disease	25 (8.9)
Peripheral vascular disease	29 (10.3)
NYHA class ≥ 3	49 (17.4)
Left ventricular dysfunction (EF < 0.50)	45 (16.0)
Coronary artery disease	78 (27.8)
EuroSCORE II	2.2 ± 2.1
STS score	2.2 ± 2.4
Atrial fibrillation	17 (6.0)
Emergent operation	3 (1.1)
Infective endocarditis	10 (3.6)

Values are presented as mean ± standard deviation or number (%).
BMI: body mass index; GFR: glomerular filtration rate; NYHA: New York Heart Association; EF: ejection fraction; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS: Society of Thoracic Surgeons.

KEY MESSAGES

- The actual lowest pump flow compared to the target pump flow based on oxygen delivery (DO$_2$) might be a predictor of postoperative acute kidney injury after cardiac surgery.
- Female sex, stroke history, emergency operation, and transfusion of red blood cells were significant risk factors of postoperative acute kidney injury after cardiac surgery.

MATERIALS AND METHODS

Patient Characteristics

The study protocol was reviewed by the Institutional Review Board of Seoul National University Hospital and approved as a minimal risk retrospective study (IRB No. H-2009-158-1159) that did not require individual consent based on the institutional guidelines for waiving consent. A total of 434 patients who underwent AVR between January 2017 and May 2020, at our institution was retrospectively screened. Patients who underwent concomitant valve surgery other than AVR (n = 40), aortic surgery under total circulatory arrest (n = 68), arrhythmia surgery (n = 32), and those with preoperative end-stage renal disease on dialysis (n = 21) were excluded. A final total of 281 patients was enrolled in the present study. The mean age at operation was 68 ± 11 years, and 160 patients (56.9%) were male. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II and Society of Thoracic Surgeons (STS) score were 2.2 ± 2.1 and 2.2 ± 2.4, respectively. Hypertension (n = 152, 54.1%), dyslipidemia (n = 116, 41.3%), diabetes (n = 79, 28.1%), and coronary artery disease (n = 78, 27.8%) were the most common comorbidities (Table 1).

Table 2. Operative data of the study patients

Variable	Total (n = 281)
Mechanical:bioprosthesis	66:215
CPB time (min)	147.4 ± 51.6
ACC time (min)	92.2 ± 32.2
Concomitant procedure	
CABG	35 (12.5)
PFO closure	12 (4.3)

Values are presented as mean ± standard deviation or number (%).
CPB: cardiopulmonary bypass; ACC: aortic cross clamp; CABG: coronary artery bypass grafting; PFO: patent foramen ovale.

Surgical Procedures

All operations were performed through median sternotomy and aorto-bicaval cannulation under moderate hypothermia (30°C–32°C). Concomitant procedures comprised coronary artery bypass grafting (n=35) and closure of patent foramen ovale (n=12). The mean CPB and aortic cross-clamp times were 147.4±51.6 and 92.2±32.2 minutes, respectively (Table 2).

Evaluation of Clinical Outcomes

The target pump flow was calculated based on DO$_2$ level of 280 ml/min/m^2 and the following equation: DO$_2$ = pump flow × (Hb concentration × Hb saturation × 1.36) + (0.003 × PaO$_2$), where Hb, hemoglobin; PaO$_2$, arterial oxygen pressure [12]. Early mortality was defined as any death within 30 days or during the same hospitalization. Postoperative atrial fibrillation was defined as a new onset or any short run of atrial fibrillation. Low cardiac output syndrome (LCOS) was defined as a cardiac index <2.0 L/min/m^2 or a systolic arterial pressure <90 mm Hg for which the patient required mechanical assistance or high inotropic support such as dopamine or dobutamine in quantities >5 μg/kg/min. Postoperative respiratory complications included pneumonia or prolonged ventilator support for more than 48 hours.

Statistical Analysis

The primary endpoint was postoperative renal dysfunction, defined as the ratio of the postoperative peak creatinine level to the preoperative value. The statistical analyses were performed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA). Continuous and dichotomous variables are expressed as the mean±standard deviation or median with interquartile range (IQR) and the number with the proportion, respectively. A paired t-test was performed to compare differences be-

Table 3. Early clinical outcomes

Variable	Total (n=281)
Early mortality	7 (2.5)
Complication	
New onset atrial fibrillation	102 (36.3)
Respiratory complications	24 (8.6)
Low cardiac output syndrome	12 (4.3)
Stroke	5 (1.8)
Complete atrioventricular block	3 (1.1)
Bleeding reoperation	3 (1.1)
Mediastinitis	1 (0.4)

Values are presented as number (%).

tween preoperative creatinine levels and postoperative peak creatinine levels.

The ratio of the actual pump flow to the target pump flow based on the DO$_2$ and the presence of other perfusion parameters during CPB such as lowest temperature, mean arterial pressure, hematocrit levels, PaO$_2$, intraoperative red blood cells (RBCs) transfusion, and preoperative characteristics were analyzed to identify factors associated with the primary endpoint. Univariate and multivariable analyses were performed using linear regression models. Variables with a P-value <0.05 in univariate analyses were entered into a multivariable model. Multi-collinearity was controlled using backward stepwise selection. The results of the multivariable analysis are expressed as *P*-value, beta coefficient (β), and standard error (SE). A P-value <0.05 was considered statistically significant.

RESULTS

Early Clinical Outcomes

The early mortality rate was 2.5% (7 of 281 patients). Postoperative complications included respiratory complications (n=24, 8.6%), LCOS (n=12, 4.3%), stroke (n=5, 1.8%), and bleeding reoperation (n=3, 1.1%) (Table 3).

CPB Variables

The lowest temperature and the lowest mean arterial pressure during CPB were 30.4°C±2.4°C and 58.9±8.8 mm Hg, respectively. The lowest hematocrit level was 21.5%±3.0%, and the median number of RBCs transfused during CPB was 0.5 (IQR, 0–1.0). Mean PaO$_2$ was 338.4±45.0 mm Hg. Based on the assumed target DO$_2$ index of 280 ml/min/m^2, the ideal target pump flow was 4.7±0.6 L/min, and the lowest actual pump

Table 4. Cardiopulmonary bypass variables

Variable	Total (n=281)
Lowest temperature (°C)	30.4±2.4
Lowest mean arterial pressure (mm Hg)	58.9±8.8
Lowest hematocrit (%)	21.5±3.0
Transfused RBC (pack)	0.5 (0–1.0)
PaO$_2$ (mm Hg)	338.4±45.0
Ideal target pump flow (L/min)	4.70±0.59
Lowest actual pump flow (L/min)	3.77±0.47
Ratio of the lowest actual pump flow to the ideal target pump flow	0.81±0.13

Values are presented as mean±standard deviation or median (interquartile range).
RBC: red blood cell; PaO$_2$: arterial oxygen pressure.

Lee Y, et al.   Effect of DO$_2$ during CPB after AVR

ACC

flow was 3.8±0.5 L/min during CPB. The ratio of the lowest actual pump flow to the ideal target pump flow was 0.81±0.13 (Table 4).

Changes in Creatinine Level after Surgery

Creatinine increased from a preoperative level of 0.94±0.33 mg/dl to a postoperative peak level of 1.15±0.56 mg/dl (P<0.001). The postoperative creatinine level was highest at postoperative day 1 (IQR, 1–2). The ratio of postoperative peak creatinine level to preoperative creatinine level was 1.22±0.33 (Table 5).

Risk Factor Analyses for the Primary Endpoint

Univariate analyses demonstrated that the ratio of the actual pump flow to the ideal target pump flow (P=0.009), age, sex, stroke history, EuroScore II, emergency status, hematocrit level, and RBC transfusion during CPB were significant factors associated with the primary endpoint. In the multivariable model, the ratio of the lowest pump flow to the maximum target pump flow (β±SE, –0.405±0.162; P=0.013), sex (reference: female; 0.193±0.045, P<0.001), stroke history (0.197±0.066, P=0.003), emergency (0.364±0.181, P=0.045), and RBC transfusion (0.099±0.033, P=0.003) were associated with the primary endpoint for postoperative renal dysfunction (Table 6).

Table 5. Changes in renal function

Variable	Value
Preoperative creatinine level (mg/dl)	0.94±0.33
Postoperative peak creatinine level (mg/dl)	1.15±0.56
Postoperative day at highest creatinine level	1 (1–2)
Ratio of postoperative to preoperative creatinine level	1.22±0.33

Values are presented as mean±standard deviation or median (interquartile range).

DISCUSSION

The present study demonstrates that the actual lowest pump flow compared to the target pump flow based on the DO$_2$ is associated with the risk of AKI after AVR. AKI is a well-recognized and clinically significant complication following cardiac surgery under CPB. The range of AKI has been reported to range from 20% to 40% of all cardiac surgical patients depending on the definition used [1-4,13,14]. Even minimal changes in postoperative creatinine values can result in both early and late morbidity and mortality after cardiac surgery [5,15-17]. Several studies have shown that AKI can exponentially increase the postoperative mortality rate to 50% in patients requiring dialysis, compared to that of 0.6% to 2% in patients with no AKI [4,18,19]. Therefore, prevention of this postoperative complication is of paramount importance.

Many studies have discovered independent risk factors leading to renal impairment after cardiac surgery [4,20-30]. However, most of the factors such as age, preoperative comorbidities, and complex surgical procedures are unmodifiable. The present study was designed to determine risk factors that could be modifiable, particularly CPB parameters. Since the incidence of AKI might vary according to type of cardiac operation [2,21,23], only patients who underwent AVR with or without coronary artery bypass graft surgery were enrolled.

Regarding CPB management, the most commonly used bypass flow rates during CPB ranged from 2.2 to 2.5 L/min/m^2 [31,32], and it has been suggested that systemic flow rates influence the perfusion of organs other than the brain. A previous prospective observational study [33] showed that low flow on CPB is the major cause of both adverse renal and neurologic outcomes. However, the optimal flow rate that supports the most favorable organ perfusion has yet to be determined, and institutional practices have been largely based on their

Table 6. Risk factor analysis for changes in creatinine level after surgery

Variable	Univariate analysis	Multivariable analysis	
	P-value	β±SE	P-value
Sex (reference: female)	0.034	0.193±0.045	<0.001
History of stroke	0.002	0.197±0.066	0.003
Emergency	0.007	0.364±0.181	0.045
Transfusion of red blood cells	0.009	0.099±0.033	0.003
Ratio of lowest actual pump flow to target pump flow	0.009	–0.405±0.162	0.013

Values are presented as mean±standard deviation. Variables in Tables 1, 2, 4, and 5 were included in the analysis, and factors that were significant in the multivariable models are shown.
SE: standard error.

own experiences. Recently, DO$_2$ has been suggested as an important modifiable parameter that prevents postoperative AKI. Two important variables for perfusion, i.e., hematocrit values and CPB pump flow rates, are incorporated into a single calculation of DO$_2$. A previous study [9], in a retrospective series, found a "critical" DO$_2$ threshold of 272 mL/min/m^2. When DO$_2$ level falls below the critical value of 260–270 mL/min/m^2, organ deoxygenation can be triggered with subsequent tissue acidosis, causing impaired postoperative renal function. Another study [11] investigated the role of potentially modifiable factors related to CPB management in determining postoperative AKI. The study results demonstrated that low DO$_2$ level during CPB is independently associated with postoperative AKI. They found that a nadir DO$_2$ less than 262 mL/min/m^2 was independently associated with development of postoperative AKI.

In the present study, based on the assumed target DO$_2$ level of 280 mL/min/m^2, the ideal target pump flow was assumed to be 4.7±0.6 L/min during CPB. Among the various CPB parameters, not the absolute value but the ratio of the nadir pump flow to the ideal target flow based on the DO$_2$ was associated with risk of AKI. In addition, the multivariable model demonstrated that not the nadir hematocrit level during CPB but transfusion was associated with AKI. The relationship between transfusion of RBCs and AKI development has long been reported in surgical literature [2,34]. However, the need for blood transfusion might be just an indicator of increased blood loss and a hypotensive or ischemic state, which is a main pathogenic mechanism of AKI. Therefore, further study is needed to clarify the impact of low hematocrit levels vs. RBC transfusion on clinical outcomes after cardiac surgery.

The present study has limitations that should be recognized. First, this was a retrospective observational study performed in a single institution. Therefore, our models must be validated at multiple centers for broader applicability. Second, the effects of unknown or unmeasured confounders associated with postoperative AKI cannot be ruled out. Finally, the number of enrolled patients in this study was relatively small. In conclusion, low actual nadir pump flow during CPB compared to the ideal target pump flow based on the DO$_2$ is associated with risk of AKI after AVR.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Yeiwon Lee   https://orcid.org/0000-0003-3342-1381
Sue Hyun Kim   https://orcid.org/0000-0002-7414-5232
Ho Young Hwang   https://orcid.org/0000-0002-8935-8118
Suk Ho Sohn   https://orcid.org/0000-0001-7391-3415
Jae Woong Choi   https://orcid.org/0000-0002-0921-756X
Kyung Hwan Kim   https://orcid.org/0000-0002-0482-9786

AUTHOR CONTRIBUTIONS

Conceptualization: SHK, HYH. Data curation: SHK, HYH. Formal analysis: SHK, HYH. Methodology: SHK, HYH. Project administration: HYH, SHS, JWC, KHK. Visualization: SHK, HYH. Writing–original draft: YL, SHK, HYH. Writing–review & editing: all authors.

REFERENCES

1. Vives M, Hernandez A, Parramon F, Estanyol N, Pardina B, Muñoz A, et al. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis 2019;12:153-66.

2. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 2009;119:495-502.

3. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. Ann Thorac Surg 2012;93:337-47.

4. Provenchère S, Plantefève G, Hufnagel G, Vicaut E, De Vaumas C, Lecharny JB, et al. Renal dysfunction after cardiac surgery with normothermic cardiopulmonary bypass: incidence, risk factors, and effect on clinical outcome. Anesth Analg 2003;96:1258-64.

5. Elmistekawy E, McDonald B, Hudson C, Ruel M, Mesana T, Chan V, et al. Clinical impact of mild acute kidney injury after cardiac surgery. Ann Thorac Surg 2014;98:815-22.

6. Sirvinskas E, Andrejaitiene J, Raliene L, Nasvytis L, Karbonskiene A, Pilvinis V, et al. Cardiopulmonary bypass management and acute renal failure: risk factors and prognosis. Perfusion 2008;23:323-7.

7. Tuttle KR, Worrall NK, Dahlstrom LR, Nandagopal R, Kausz AT, Davis CL. Predictors of ARF after cardiac surgical procedures. Am J Kidney Dis 2003;41:76-83.

8. Bastin AJ, Ostermann M, Slack AJ, Diller GP, Finney SJ, Evans TW. Acute kidney injury after cardiac surgery according to Risk/Injury/Failure/Loss/End-stage, Acute Kidney Injury

Lee Y, et al.   Effect of DO₂ during CPB after AVR

ACC

Network, and Kidney Disease: Improving Global Outcomes classifications. J Crit Care 2013;28:389-96.

9. Ranucci M, Romitti F, Isgrò G, Cotza M, Brozzi S, Boncilli A, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg 2005; 80:2213-20.

10. Magruder JT, Dungan SP, Grimm JC, Harness HL, Wierschke C, Castillejo S, et al. Nadir oxygen delivery on bypass and hypotension increase acute kidney injury risk after cardiac operations. Ann Thorac Surg 2015;100:1697-703.

11. de Somer F, Mulholland JW, Bryan MR, Aloisio T, Van Nooten GJ, Ranucci M. O2 delivery and CO2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? Crit Care 2011;15:R192.

12. Murphy GS, Hessel EA 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesth Analg 2009;108:1394-417.

13. Brown JR, Cochran RP, MacKenzie TA, Furnary AP, Kunzelman KS, Ross CS, et al. Long-term survival after cardiac surgery is predicted by estimated glomerular filtration rate. Ann Thorac Surg 2008;86:4-11.

14. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009; 119:2444-53.

15. Liotta M, Olsson D, Sartipy U, Holzmann MJ. Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting. Am J Cardiol 2014;113:70-5.

16. Tolpin DA, Collard CD, Lee VV, Virani SS, Allison PM, Elayda MA, et al. Subclinical changes in serum creatinine and mortality after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2012;143:682-8.

17. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004;15:1597-605.

18. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, et al. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011;15:R16.

19. Thakar CV, Worley S, Arrigain S, Yared JP, Paganini EP. Influence of renal dysfunction on mortality after cardiac surgery: modifying effect of preoperative renal function. Kidney Int 2005;67:1112-9.

20. Rosner MH, Okusa MD. Acute kidney injury associated with

cardiac surgery. Clin J Am Soc Nephrol 2006;1:19-32.

21. Wijeysundera DN, Karkouti K, Dupuis JY, Rao V, Chan CT, Granton JT, et al. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA 2007;297:1801-9.

22. Palomba H, de Castro I, Neto AL, Lage S, Yu L. Acute kidney injury prediction following elective cardiac surgery: AKICS Score. Kidney Int 2007;72:624-31.

23. Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, et al. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation 2006;114:2208-16.

24. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.

25. Grayson AD, Khater M, Jackson M, Fox MA. Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg 2003;75:1829-35.

26. Eriksen BO, Hoff KR, Solberg S. Prediction of acute renal failure after cardiac surgery: retrospective cross-validation of a clinical algorithm. Nephrol Dial Transplant 2003;18:77-81.

27. Janssen DP, Noyez L, van Druten JA, Skotnicki SH, Lacquet LK. Predictors of nephrological morbidity after coronary artery bypass surgery. Cardiovasc Surg 2002;10:222-7.

28. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998; 128:194-203.

29. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, et al. Preoperative renal risk stratification. Circulation 1997;95:878-84.

30. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 2006;81:542-6.

31. DeFoe GR, Ross CS, Olmstead EM, Surgenor SD, Fillinger MP, Groom RC, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg 2001;71:769-76.

32. Cook DJ, Proper JA, Orszulak TA, Daly RC, Oliver WC Jr. Effect of pump flow rate on cerebral blood flow during hypothermic cardiopulmonary bypass in adults. J Cardiothorac Vasc Anesth 1997;11:415-9.

33. Slogoff S, Reul GJ, Keats AS, Curry GR, Crum ME, Elmquist BA, et al. Role of perfusion pressure and flow in major organ

dysfunction after cardiopulmonary bypass. Ann Thorac Surg 1990;50:911-8.

34. Bove T, Calabrò MG, Landoni G, Aletti G, Marino G, Crescenzi G, et al. The incidence and risk of acute renal failure after cardiac surgery. J Cardiothorac Vasc Anesth 2004;18:442-5.