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Effects of cardiopulmonary bypass perfusion temperature on perioperative renal function in adult patients undergoing cardiac surgery

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Cover Page Footnote

Aims and objective: The primary objective of this investigation was to study the effects of cardiopulmonary bypass (CPB) perfusion temperature on renal function parameters [serum creatinine, creatinine clearance, urine albumin, urine protein, and urine albumin/creatinine ratio (ACR)]. The secondary objective was to detect renal complications of CPB. Materials and methods: This is a prospective longitudinal study of 30 adult patients (17 men, 13 women; mean age, 53.37 ± 16.02 years) who underwent valvular heart surgery [with or without coronary artery bypass grafting (CABG)]. Serum creatinine, creatinine clearance, urine protein, urine albumin, and urine ACR were collected during CPB (at 28 C, 32 C, and 37 C) and postoperatively (at 12 hours, 24 hours, and 48 hours). Data were analyzed using one-way repeatedmeasures analysis of variance (ANOVA). A significant ANOVA was followed by a BonferronieHolm post hoc test. Results: Although serum creatinine ($p < 0.001$) and creatinine clearance (p¼0.0016) underwent a significant ANOVA change ($p < 0.001$ and p¼0.0016, respectively) after CPB, there was no statistically significant change compared with their baseline values. Urine ACR showed a significant change at 28 C ($p < 0.01$), 32 C ($p < 0.01$), and 37 C ($p < 0.05$) as compared with baseline values. No significant change in urine albumin was observed during CPB or up to 24 hours. A significant change occurred after 48 hours of CPB ($p < 0.05$). A significant increase in urine protein was noted after CPB at 12 hours ($p < 0.01$), 24 hours ($p < 0.01$), and 48 hours ($p < 0.01$). Overall, 12 (40%) patients had acute kidney injury (AKI). Ten (33.33%) patients had stage I AKI, one patient progressed to AKI stage II, and another to AKI stage III. Of the 10 patients who had stage I AKI, eight had complete recovery within 48 hours. Conclusions: CPB with moderate hypothermia for valvular heart surgeries can be performed safely in patients with adequate renal functional reserve. The glomerular permeability across the Bowman's capsule increases after CPB as evidenced by significant proteinuria at 12 hours and increased albuminuria at 48 hours after surgery. There is an increased risk of transient stage I AKI after CPB, from which patients recover within 48 hours.

ORIGINAL ARTICLE

Effects of cardiopulmonary bypass perfusion temperature on perioperative renal function in adult patients undergoing cardiac surgery

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Abstract

Aims and objective: **The primary objective of this investigation was to study the effects of cardiopulmonary bypass (CPB) perfusion temperature on renal function parameters [serum creatinine, creatinine clearance, urine albumin, urine protein, and urine albumin/creatinine ratio (ACR)]. The secondary objective was to detect renal complications of CPB.**

Materials and methods: **This is a prospective longitudinal study of 30 adult patients (17 men, 13 women; mean age, 53.37 ± 16.02 years) who underwent valvular heart surgery [with or without coronary artery bypass grafting (CABG)]. Serum creatinine, creatinine clearance, urine protein, urine albumin, and urine ACR were collected during CPB (at 28 °C, 32 °C, and 37 °C) and postoperatively (at 12 hours, 24 hours, and 48 hours). Data were analyzed using one-way repeated-measures analysis of variance (ANOVA). A significant ANOVA was followed by a Bonferroni–Holm *post hoc* test.**

Results: **Although serum creatinine ($p < 0.001$) and creatinine clearance ($p = 0.0016$) underwent a significant ANOVA change ($p < 0.001$ and $p = 0.0016$, respectively) after CPB, there was no statistically significant change compared with their baseline values. Urine ACR showed a significant change at 28 °C ($p < 0.01$), 32 °C ($p < 0.01$), and 37 °C ($p < 0.05$) as compared with baseline values. No significant change in urine albumin was observed during CPB or up to 24 hours. A significant change occurred after 48 hours of CPB ($p < 0.05$). A significant increase in urine protein was noted after CPB at 12 hours ($p < 0.01$), 24 hours ($p < 0.01$), and 48 hours ($p < 0.01$). Overall, 12 (40%) patients had acute kidney injury (AKI). Ten (33.33%) patients had stage I AKI, one patient progressed to AKI stage II, and another to AKI stage III. Of the 10 patients who had stage I AKI, eight had complete recovery within 48 hours.**

Conclusions: **CPB with moderate hypothermia for valvular heart surgeries can be performed safely in patients with adequate renal functional reserve. The glomerular permeability across the Bowman's capsule increases after CPB as evidenced by significant proteinuria at 12 hours and increased albuminuria at 48 hours after surgery. There is an increased risk of transient stage I AKI after CPB, from which patients recover within 48 hours.**

Keywords: Acute kidney injury, Albuminuria, Cardiopulmonary bypass, Cardiac, Creatinine, Creatinine clearance, Heart valves, Hypothermia, Perfusion cardiac

1. Introduction

The prevalence of acute kidney injury (AKI) after cardiac surgery is as high as 30%. This is associated with increased mortality and morbidity [1,2]. It prolongs hospital stay and leads to significant economic burden [3]. Even a modest increase in serum creatinine values (0.3–0.5 mg/dL) significantly increases early mortality after cardiac surgery [4,5].

This study was designed to investigate the influence of cardiopulmonary bypass (CPB) perfusion

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temperature on the perioperative renal function of adult patients undergoing valvular heart surgeries. We analyzed the effects of hypothermia and subsequent rewarming on renal function.

2. Materials and methods

This investigation was designed as a prospective longitudinal study of 30 adult patients (17 men and 13 women; mean age, 53.37 ± 16.02 years) who underwent valvular heart surgery (with or without CABG) at a tertiary cardiac care center between March 2019 and May 2019. Patients aged between 19 years and 70 years with a normal baseline renal function were included. Patients with diabetes mellitus, serum creatinine level ≥1.4 mg/dL, preoperative abnormal urinalysis, ventricular dysfunction, intraoperative surgical complications, reexploration, and those requiring inotropic supports for more than 24 hours were excluded from further study. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all participants.

Serum creatinine, urine total protein, urine albumin, and urine albumin/creatinine ratio (ACR) of all patients were collected a day prior to the surgery. Creatinine clearance was calculated using the Cockroft−Gault formula [6].

Anesthetic techniques were standardized for all patients. All surgeries were performed through a midline sternotomy. Heparin 400 IU/kg was administered intravenously. CPB was initiated when the activated clotting time exceeded 480 seconds. Extracorporeal circulation was performed using a Sorin inspire adult membrane oxygenator (Sorin Group, LivaNova USA Inc.,14401 West 65th Way, Arvada, CO 80004-3599), Sarns 8000 perfusion pump (Terumo Cardiovascular Systems Corporation, 6200 Jackson Road, Ann Arbor MI 48103-9586) and a Spictra AF arterial line filter (Meddevices Lifesciences B.V, Kraijenhoffstraat 137A,1018RG Amsterdam The Netherlands). Nonpulsatile perfusion was maintained at a flow rate of 2.2−2.4 L/m^2/min. The bypass circuit was primed using 1 L Plasmalyte A solution (Baxter SL - Bieffe Medital SA, Biescas road, Senegue, s/n, 22666 Sabinanigo), 3 mg/kg 10% mannitol, and 10,000 IU heparin.

Hematocrit was maintained between 20% and 25% (packed red cells were added if necessary). Mean arterial pressure (MAP) of 40−60 mmHg was maintained throughout CPB. Acid−base management was by the alpha-stat principle.

All patients were cooled down to a nasopharyngeal temperature of 28 °C. After aortic cross-clamp, myocardial protection was achieved with intermittent antegrade cold blood cardioplegia (delivered at 4 °C). Ten minutes prior to the release of aortic cross-clamp, rewarming was initiated. Patients were rewarmed to 37 °C. Heparinization was reversed with an injection protamine sulfate (1−1.3 mg for every 100 IU of heparin). Patients were weaned off CPB with stable hemodynamics. Patients were transferred to the cardiac intensive care unit after surgery.

The following data were collected during CPB (at 28 °C, 32 °C, and 37 °C) and postoperatively (at 12 hours, 24 hours, and 48 hours). Serum creatinine, creatinine clearance, urine protein, urine albumin, and urine ACR were analyzed.

Age, height, weight, body surface area, CPB time, aortic cross-clamp time, type of surgery, and average perfusion flow rates of the patients were documented.

Occurrence of AKI was documented as per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. A diagnosis of AKI Stage I was made if serum creatinine increased by 0.3 mg/dL or more within 48 hours or elevated to 1.5 times the baseline value. A diagnosis of AKI stage II was made if serum creatinine increased by 2−2.9 times the baseline value. A diagnosis of AKI stage III was made if serum creatinine increased by 3.0 times the baseline value [7].

In this study, full recovery from AKI was defined as absence of AKI criteria at 48 hours after CPB.

Abbreviations

ACR	Albumin Creatinine Ratio
ANOVA	Analysis of variance
CPB	Cardiopulmonary bypass
AKI	Acute Kidney Injury
MAP	Mean arterial pressure
KDIGO	Kidney Disease Improving Global Outcomes
CABG	Coronary artery bypass graft
GFR	Glomerular functional rate

2.1. Statistical analysis

Descriptive and inferential statistics were used to analyze the data collected. The parametric variables were analyzed by calculating presented as mean ± standard deviation (SD). Data were analyzed by one-way repeated-measures analysis of variance (ANOVA). A significant ANOVA was followed by a Bonferroni−Holm *post hoc* test for comparison of baseline (pre-CPB) values versus data from subsequent measuring points (at 28 °C, 32 °C, and 37 °C and 12 hours, 24 hours, and 48 hours after

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CPB). Data are presented as mean ± SD. The data obtained during CPB and thereafter were pooled. A p value <0.05 was considered statistically significant. Box-and-whisker plots were made with the lowest value, highest value, 25th percentile, median, and 75th percentile. Statistical analysis was performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) version 23 software.

3. Results

The surgical procedures carried out are listed in Table 1. The mean body surface area of the patients was $1.68 \pm 0.19\ m^2$. The mean systemic perfusion flow rate during CPB was 2.69 ± 0.31 L/min. The mean CPB duration was 108.50 ± 30.76 minutes, and the mean aortic cross clamp time was 76.67 ± 24.06 minutes.

The study showed that serum creatinine underwent a significant ANOVA change ($p < 0.001$). A Bonferroni–Holm *post hoc* test was done for comparing intergroup variability of data collected at different time points [preoperatively, during CPB (at 28 °C, 32 °C, and 37 °C), after CPB (at 12 hours, 24 hours, and 48 hours)]. None of the groups showed any statistically significant variability when compared with the preoperative baseline serum creatinine values (Table 2 and Fig. 1).

Similarly, serum creatinine clearance showed a significant ANOVA change ($p = 0.0016$). However, a Bonferroni–Holm *post hoc* test revealed no statistically significant change as compared to baseline serum creatinine clearance values in any of the groups (Table 2 and Fig. 2).

Urine ACR showed a significant change ($p < 0.001$, ANOVA). Bonferroni–Holm *post hoc* test showed a significant change in ACR at 28 °C ($p < 0.01$), 32 °C ($p < 0.01$), and at 37 °C ($p < 0.05$) as compared to baseline values. Subsequent values showed no statistically significant changes with respect to baseline (Table 2 and Fig. 3).

Table 1. Surgical procedure.

Surgical procedure	Patients ($N = 30$)
Mitral valve replacement (MVR)	4
Aortic valve replacement (AVR)	13
Double valve replacement (DVR)	3
Mitral valve repair	3
Mitral valve repair with tricuspid valve repair	1
CABG with AVR	3
CABG with MVR	1
CABG with mitral valve repair	1
AVR with mitral valve repair	1

CABG, coronary artery bypass grafting.

Table 2. Systemic variables.[a]

Variable	Preoperative value	At 28 °C	At 32 °C	At 37 °C	At 12 h	At 24 h	At 48 h	p (ANOVA)
Serum creatinine (mg/dL)	0.81 ± 0.16	0.70 ± 0.19	0.71 ± 0.20	0.71 ± 0.19	0.97 ± 0.25	0.94 ± 0.37	0.88 ± 0.39	<0.001
Creatinine clearance (mL/min)	91.16 ± 23.01	107.65 ± 30.89	105.12 ± 30.38	105.95 ± 29.85	78.01 ± 24.66	87.38 ± 39.31	91.64 ± 37.48	0.0016
Total urine protein (mg/dL)	1.82 ± 1.51	5.66 ± 11.78	5.96 ± 8.21	3.86 ± 2.80	21.10 ± 11.53**	26.69 ± 16.90**	32.62 ± 24.12**	<0.001
Urine albumin (mg/L)	9.76 ± 10.61	32.05 ± 84.43	25.38 ± 53.96	11.96 ± 15.86	25.68 ± 25.17	41.94 ± 38.66	49.49 ± 57.35*	0.0144
Urine albumin/creatinine ratio (μg/mg creatinine)	24.00 ± 8.52	158.07 ± 166.81**	124.5 ± 128.05**	122.86 ± 195.75*	70.80 ± 81.10	75.50 ± 69.91	81.96 ± 79.69	<0.001

ANOVA = analysis of variance; SD = standard deviation.

[a] Values are presented as mean ± SD. Bonferroni–Holm adjustment for multiple comparisons was used.

* $p < 0.05$ versus baseline.

** $p < 0.01$ versus baseline.

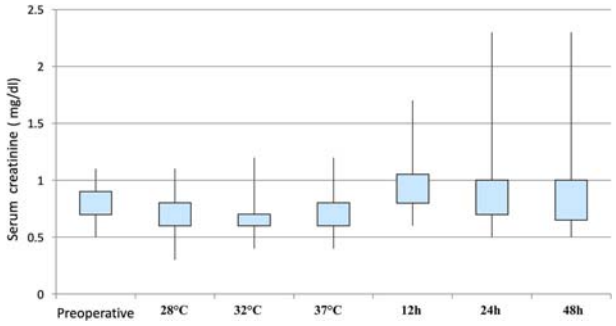

Fig. 1. Box-and-whisker plots of serum creatinine values (in mg/dL) during the study. Each chart bar represents the point at which data were analyzed (during CPB at 28 °C, 32 °C, and 37 °C and after CPB at 12 hours, 24 hours, and 48 hours). Boxes represent median values with interquartile range. Lower limit of the box represents the 25th percentile. Upper limit of the box represents the 75th percentile. The ends of whiskers represent the minimum and maximum of all of the data. CPB, cardiopulmonary bypass.

Urine protein showed a significant change ($p < 0.001$, ANOVA). Bonferroni–Holm *post hoc* test showed a significant change after CPB at 12 hours ($p < 0.01$), 24 hours ($p < 0.01$), and 48 hours ($p < 0.01$). However, no significant change was observed during CPB (Table 2).

Urine albumin showed a significant change ($p = 0.014$, ANOVA). Bonferroni–Holm *post hoc* test showed a significant change 48 hours after CPB ($p < 0.05$). No significant change in urine albumin was observed during or up to 24 hours after CPB.

Twelve (40%) patients had AKI as per KDIGO guidelines. Ten (33.33%) patients had stage I AKI, one patient progressed to AKI stage II, and another patient progressed to AKI stage III. None of the patients required hemodialysis. The patient who progressed to AKI stage II recovered within 7 days. The patient in AKI stage III recovered in 3 weeks. Of the 10 patients who had stage I AKI, eight (80%) patients had complete recovery within 48 hours.

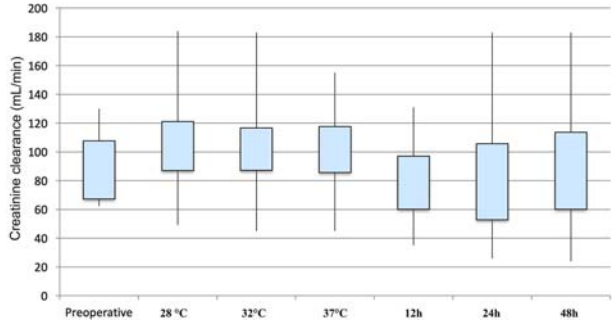

Fig. 2. Box-and-whisker plots of serum creatinine clearance values (in mL/min) during the study. Each chart bar represents the point at which data were analyzed (during CPB at 28 °C, 32 °C, and 37 °C and after CPB at 12 hours, 24 hours, and 48 hours). Boxes represent median values with interquartile range. Lower limit of the box represents the 25th percentile. Upper limit of the box represents the 75th percentile. The ends of whiskers represent the minimum and maximum of all of the data. CPB, cardiopulmonary bypass.

4. Discussion

The pathophysiology of postoperative renal dysfunction after cardiac surgery is multifactorial. It is most commonly attributed to CPB [8].

The nonpulsatile nature of blood flow during CPB activates the renin–angiotensin–aldosterone axis. It upsets the balance between renal cortical and medullary perfusion [9–11]. Overall, 20% of the cardiac output goes into perfusion of kidneys. During CPB, the majority of this blood is shunted away from the vasa recta to renal cortex. Consequently, the renal medulla is hypoxic in relation to other tissues, making it prone to ischemia [12].

The duration of CPB, aortic cross-clamp time, hemodilution, microemboli, and hypoperfusion of kidneys are significant risk factors for AKI [13–15]. The inflammatory cytokines, ischemic reperfusion, and oxidative damage of CPB add to the cumulative deleterious effects on the kidney [16–18]. The components of CPB circuit such as the pump, tubings, and oxygenator contribute to hemolysis and release of free hemoglobin. Free hemoglobin depletes haptoglobin, catalyzes the generation of free radicals, and contributes to AKI [19–22].

Hypothermia during CPB is a commonly used strategy to reduce metabolic rate and ischemic stress. The effects of hypothermia and rewarming during CPB were analyzed by two randomized studies of patients undergoing CABG. They concluded that CPB perfusion temperature had no significant effect on perioperative renal function [23,24]. However, a study by Boodhwani et al [25] concluded that the rewarming process was an independent risk factor for AKI. Meanwhile, animal studies have offered a possible explanation. Kidney with its high reperfusion rewarms faster than the brain. Consequently, the actual renal temperature might exceed the monitored nasopharyngeal temperature [26,27].A recent multicentric study concluded that the duration of hyperthermic perfusion >37 °C is an independent predictor of AKI after CPB [28].

The above studies showed contradictory clinical results. Moreover, they used different criteria for defining AKI. To address the discrepancies, we carried out this study to throw more light into the effect of the rewarming phase of CPB on kidneys. Most of the above studies were performed on

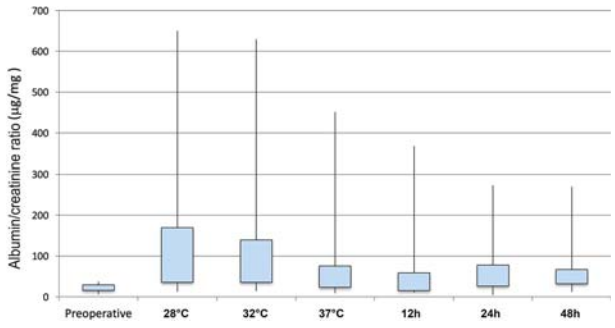

Fig. 3. Box-and-whisker plots of urine albumin/creatinine ratio (in µg/mg) values during the study. Each chart bar represents the point at which data were analyzed (during CPB at 28 °C, 32 °C, and 37 °C and after CPB at 12 hours, 24 hours, and 48 hours). Boxes represent median values with interquartile range. Lower limit of the box represents the 25th percentile. Upper limit of the box represents the 75th percentile. The ends of whiskers represent the minimum and maximum of all of the data. CPB, cardiopulmonary bypass.

patients who underwent CABG, whereas our study was performed on a cohort of patients who underwent valvular heart surgery (with or without CABG) with normal baseline renal function.

Our study monitored the varying trends of urinary protein, urinary albumin, urine ACR, serum creatinine, and creatinine clearance from the initiation of CPB until 48 hours after the procedure.

A normal baseline glomerular functional rate (GFR) does not reflect the renal functional reserve and the true functional status of the kidney. A lower preoperative renal functional reserve despite having normal GFR is a risk factor for developing AKI after cardiac surgery [29]. Kidneys with good renal functional reserve respond to stress during CPB by increasing GFR [30]. Although statistically not significant, our study showed increased creatinine clearance during CPB leading to a transient decrease in serum creatinine levels (Table 2).

ACR and proteinuria are important biomarkers of AKI after cardiac surgery [31]. When the ability of kidneys for tubular resorption of proteins is saturated, even a minor increase in glomerular permeability during CPB leads to significant albuminuria. Thus, urinary albumin acts as a reliable indicator of glomerular damage. Our study documented significant proteinuria after 12 hours ($p < 0.01$) and significant albuminuria after 48 hours of CPB ($p < 0.05$) (Table 2).

Serial daily monitoring of ACR provides valuable data regarding risk of progression of AKI. ACR >133 mg/g at the time of AKI diagnosis had a 3.4 times the odds of AKI progression in comparison with ACR <35 mg/g [32]. Our study documented a significant rise in urine ACR during CPB (Table 2). Newer biomarkers for early detection of AKI are available. But with the widespread availability and decreased assay cost of ACR, the routine measurement of ACR after cardiac surgery is warranted.

The KDIGO definition is the most commonly used definition for cardiac surgery-associated AKI. This criterion was used to define and stage AKI in our study. Overall, 66% of patients who develop AKI after cardiac surgery manifest it within the first 48 hours [32].

A large proportion of our patients (40%) had AKI after CPB. Most of them had stage I AKI and recovered within 48 hours.

5. Conclusion

CPB with moderate hypothermia for valvular heart surgeries can be performed safely in patients with adequate renal functional reserve. CPB does put a stress on the kidneys to enhance its GFR as evidenced by increased serum creatinine clearance values, which return to baseline within 48 hours. The glomerular permeability across the Bowman's capsule increases after CPB as evidenced by significant proteinuria at 12 hours and increased albuminuria at 48 hours after surgery. These findings need to be reconfirmed in future prospective longitudinal studies with larger sample sizes. The incidence of AKI is as high as 40% in our study. Most of these patients had transient stage I AKI that reverted to normal within 48 hours of CPB with conservative management. A very small subset of patients progressed to AKI stages II and III with a delayed recovery of renal function.

Conflicts of interest

The authors declare that they have no conflict of interest.

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