

## Original Article

## Effect of Hypothermia During Cardiopulmonary Bypass on Neurocognition After Cardiac Surgery in Adults

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## Abstract

**Background:** The use of Hypothermia during Cardiopulmonary bypass (CPB) is a beneficial approach regarding neurocognitive protection to the patients, but at the same time, the added effects of hypothermia also carry some potential adverse outcomes.

**Objective:** To compare the effects of mild and moderate hypothermia during cardiopulmonary bypass on post-operative neurocognitive function in patients undergoing elective cardiac surgeries.

**Methods:** Patients undergoing on-pump Cardiac Surgery were assigned to the two groups according to the degree of hypothermia they received. The two groups, namely, mild hypothermia (31 °C to 35 °C) and moderate hypothermia (25 °C to 30 °C). Each group has thirty patients. The Mini-Mental State Examination (MMSE) is a standardized 30-point cognitive assessment tool, selected for this study due to its validated reliability in detecting post-operative neurocognitive decline, and was administered both pre-operatively and post-operatively.

**Results:** A total of 72 patients were received for Cardiac Surgery, out of which 60 (83.3%) patients met our inclusion criteria and underwent elective cardiac surgery using CPB by the same surgeon, and other team members. The study found no significant difference in post-operative neurocognitive decline between the mild and moderate hypothermia groups when comparing their post-operative MMSE scores. We found no significant difference in blood loss, hours of ventilation and inotropic support. However, the adrenaline infusion rate with the mild hypothermia group exhibited a slightly higher value while the ICU stay with moderate hypothermia was longer compared to those with mild hypothermia group (p-value of 0.045).

**Conclusion:** Our study demonstrates that the use of either mild or moderate hypothermia during CPB resulted in no significant difference in postoperative neurocognitive function. However, the duration of stay in the ICU and inotropic support in terms of adrenaline infusion rate varied among the groups, indicating that patients may recover differently depending on whether they received mild or moderate hypothermia during CPB.

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## Introduction

Cardiac surgery carries significant risks, though outcomes have improved over time. The Society of Thoracic Surgeons reported CABG mortality dropped from 2.6% (1998) to 1.8% (2021), with complications

decreasing from 35% to 11.4%.<sup>1</sup> Cardiac surgery utilizing cardiopulmonary bypass (CPB) remains the gold standard for treating complex cardiovascular diseases, with approximately 1 million procedures performed annually worldwide.<sup>2</sup> The development of CPB was a real blessing for cardiac surgery, but the possible negative impact on the perfused internal organs should not be neglected.<sup>3</sup>

Hypothermic cardiopulmonary bypass is frequently applied in the cardiac surgery practice where lowering body temperature confer invaluable protection to the critical tissues especially the myocardium and brain. This technique decreases oxygen needs over times of absent or reduced blood circulation, thereby preventing ischemic harm in the process, by slowing down metabolic rate.<sup>4</sup> Moreover, this metabolic injury conserves cellular ATP stores and reduces reperfusion related oxidative injury making hypothermia a dual neuro protective and cardio protective intervention in contemporary cardiac surgery.<sup>5</sup> The perfusion team has a significant duty in regulating the various physiological variables that are kept constant in case of cardiopulmonary bypass.<sup>6</sup> The existing body of literature shows that there is a wide range of practices on temperature control, and there is no agreement in all surgical centers on the best practices.<sup>7</sup>

A significant issue that is related to cardiovascular surgery is cognitive dysfunction.<sup>8</sup> Cognitive dysfunction is estimated to occur in 30 percent to 80 percent of cardiac surgical patients.<sup>9</sup> The condition can be short term or long term and result in permanent disabilities. The neurologic problems after cardiac surgery may be mild cognitive impairment to severe events such as stroke or mortality.<sup>10</sup> To reduce and prevent these events, it is important to take into account what factors can trigger such outcomes.

Out of the many risk factors known to induce cognitive dysfunction after cardiac surgery the use of hypothermia during CPB remains the most controversial.<sup>11</sup> Hypothermia, despite being a widely used technique over the years for multi-organ protection, is still filled with doubts between its merits and demerits.<sup>12</sup> The link between hypothermia and neurocognitive dysfunction remains unclear due to inconsistent data. Identifying its root cause could aid in developing effective treatment strategies and preventive measures.<sup>13</sup>

In this study, the Mini-Mental State Examination (MMSE), a reliable, friendly, and time-efficient test for assessing the cognitive domains, will be used in a number of cardiac surgical procedures.

Postoperative neurocognitive dysfunction remains a clinically relevant complication following cardiac surgery performed with CPB. Even though hypothermia is also commonly utilized in CPB to offer cerebral and myocardial protection, its effects on postoperative neurocognitive outcomes are controversial because the evidence is diverse. It is important to clarify the extent to which various levels of hypothermia have different effects on the level of cognitive functioning and early postoperative recovery parameters to optimize temperature management policies. Hence, the research question was to compare the impact of mild and moderate hypothermia during CPB on the postoperative neurocognitive performance, and the chosen secondary clinical outcomes, in adult surgical patients undergoing elective cardiac surgery.

## Methods

The study was a prospective cohort study that was done in the Department of Cardiac Surgery, King Edward Medical University/Mayo Hospital, Lahore, a large tertiary care facility in Pakistan. On February 15, 2023, the review board of the institution gave an ethical approval on the study (Ref: 129/RC/ KEMU/ 2023). This study was approved to take six months and in the process, there were 72 cardiac surgical patients. Patients with prior cerebrovascular or psychological disease, present infections or emergencies, those that have undergone Off Pump Coronary Artery Bypass Grafting (OPCABG) and illiterate persons were excluded. The Mini-Mental State Examination (MMSE) is a 30 point cognitive test that is standardized because it has been shown to be dependable in identifying post-surgery neurocognitive decline. The study included adult patients (30-60 years) undergoing elective on-pump cardiac surgery with hypothermia and a pre-operative MMSE score of 24 or higher, indicating no prior neurocognitive deficits. Temperature allocation was performed preoperatively using sealed opaque envelopes prepared by an independent investigator who was not involved in patient management or outcome assessment. Hence with this method the operating surgeon decided for the assigned temperature range immediately prior to initiation of cardiopulmonary bypass and adhered to the allocated target temperature throughout the procedure. Patients were divided by the level of hypothermia they received, with two groups: mild hypothermia (31°C - 35°C) or moderate hypothermia (25°C - 30°C).<sup>14,15</sup> The sample size was calculated a priori based on the primary outcome of postoperative neurocognitive function assessed using the Mini-Mental State Examination (MMSE). Assuming a mean diffe-

rence of 2 points in postoperative MMSE scores between groups, with a standard deviation of 2.5, a two-sided alpha level of 0.05, and a study power of 80%, the minimum required sample size was calculated to be 27 patients per group. To account for potential dropouts and incomplete data, 30 patients were recruited in each group, resulting in a total sample size of 60 participants. Hence, Out of the 72 patients, 60 met our inclusion criteria: 47 (78.33%) underwent Coronary Artery Bypass Grafting (CABG), 8 (13.33%) underwent Mitral Valve Replacement (MVR), and 5 (8.33%) underwent Double Valve Replacement (DVR). Thirty patients were included in each hypothermic group. Preoperative and postoperative MMSE assessments were performed by trained professionals on patients undergoing cardiac surgery. All participants provided informed consent. Patient demographics and baseline blood parameters (liver enzymes, blood urea, CBC) were recorded. A trained professional conducted and documented the preoperative MMSE.

The same surgical team performed all surgeries. A median sternotomy approach was used with CPB, and patients randomly underwent mild or moderate hypothermia. Standard perfusion protocols were followed, and temperature was recorded at the nasopharyngeal site. Patients were put under general anesthesia. The CPB circuit was prepped by using 1.2 to 1.8 L of isotonic solution (Hartmann's), making the circuit air-free. Additionally, we added mannitol (0.25 g/kg) and porcine heparin (3 IU/mL). All cases were performed using a roller pump (Maquet, HL-20, Harlingen, Germany) and a hollow fiber adult membrane oxygenator (Sorin Inspire Liva Nova, London, UK) at perfusion flow rates of 2.4 L/min/m<sup>2</sup> of body surface area. Cooling began after aortic cross-clamp placement, and Del Nido-based microplegia was administered for cardiac arrest. The CPB time, ACC time, and level of hemodilution by hemoglobin status were also recorded. The Activated clotting time (ACT) was recorded pre-operatively, after heparin administration, every 30 minutes during CPB and after protamine administration.

Following admission to the ICU, post-operative labs, the duration of ventilation, length of ICU stay, blood loss and inotropic support were recorded. The MMSE was performed two days following the surgery to ensure that the patient was capable of being assessed.

Statistical analysis was performed using SPSS version 26. The Shapiro-Wilk test assessed data normality. Quantitative variables are presented as mean  $\pm$  SD or median (range) for non-normal data, while qualitative variables are shown as frequency and percentage.

Independent t-test or Mann-Whitney U test compared means/medians based on distribution, and Pearson's chi-squared test analyzed categorical variables. For key outcome measures, effect estimates are reported alongside 95% confidence intervals (CIs) to provide an indication of the precision of the observed differences between groups. A p-value <0.05 was considered statistically significant.

## Results

A total of 72 patients underwent cardiac intervention, out of which 60 (83.3%) patients met our inclusion criteria and underwent elective cardiac surgery. Thirty patients in each group were included. Table 1 below showcases the distribution of the surgical procedures among the hypothermic groups.

**Table 1:** Classification of surgical operations among hypothermic categories.

Operation	Degree of Hypothermia		Total n (%)	P-Value
	Moderate n (%)	Mild n (%)		
Coronary artery bypass grafting (CABG)	23 (76.7)	24 (80)	47 (78.33)	0.884
Mitral valve replacement (MVR)	4 (13.3)	4 (13.3)	8 (13.33)	1.000
Double valve replacement (DVR)	3 (10)	2 (6.7)	5 (8.33)	0.655
Total	30 (50)	30 (50)	60 (100)	0.895

Moderate hypothermia (25-30 °C) and moderate hypothermia (30-35 °C). The data are reported as n = number of patients and percentage, and the p-value is calculated using Pearson's chi-squared test.

The patient's basal characteristics, along with preoperative baseline values, are presented in Table 2. All the parameters were similar in both except SGPT (p = 0.020) and Hb (p = 0.028).

Moderate hypothermia range (25°C - 30°C), Mild hypothermia range (30°C - 35°C). Data are presented as "n" for patient count and percentage, with values given as mean  $\pm$  SD and median (range). Abbreviations include SGPT (Serum glutamic pyruvic transaminase), SGOT (Serum glutamic oxaloacetic transaminase)

Moderate hypothermia range (25°C - 30°C), Mild hypothermia range (30°C - 35°C). Data are presented as "n" for patient count and percentage, with values given as mean  $\pm$  SD and median (range). Abbreviations include SGPT (Serum glutamic pyruvic transaminase), SGOT (Serum glutamic oxaloacetic transaminase), and ACC (Aortic cross-clamp time).

A p-value of 0.687 was obtained when comparing post-

**Table 2:** Pre-operative parameters of patients

Parameter	Types of Hypothermia		p-value
	Moderate (n=30)	Mild (n=30)	
<b>Preoperative Phase</b>			
Age (years)	52.5 (45-56)	50.5(40-56.2)	0.657
Gender; male; n (%)	25 (83.3)	21 (70)	0.522
History of diabetes mellitus; n (%)	18 (60)	15 (50)	0.436
History of smoking; n (%)	14 (46.7)	14 (46.7)	1.000
Hypertensive; n (%)	20 (66.7)	16 (53.3)	0.292
Weight (kg)	66.1±13.3	68.6±16.09	0.520
Height (cm)	164 (157.7-168)	167.5 (161.2-172)	0.139
Body mass index (kg/m <sup>2</sup> )	25.3 (22.2-27.6)	25.8 (21.9-30.2)	0.717
Ejection fraction (%)	55 (35-67)	55 (35-65)	0.994
Blood urea (mg/dL)	28 (22-33.5)	23.5 (17.7-30.2)	0.026
Serum creatinine (mg/dL)	0.90 (0.80-1.10)	0.90 (0.77-1.02)	0.327
SGPT (U/L)	32 (16-63)	24 (12-83)	0.020
SGOT (U/L)	25 (16-112)	26 (15-67)	0.912
Hb (g/dL)	14.3±2.25	13±2.41	0.028
TLC (10 <sup>3</sup> /μL)	8.60 (6.84-9.52)	9.06 (7.65-10.96)	0.098
PLT (10 <sup>3</sup> /μL)	251.5 (219.5-304.2)	251 (202-296.2)	0.796
Preoperative MMSE score	25.5 (25-27)	25 (24-27)	0.524

operative MMSE scores between the mild and moderate hypothermia groups. The observed mean difference was small, and the 95% confidence interval crossed zero, indicating no statistically significant difference in postoperative neurocognitive function between the two temperature strategies.

No significant difference was found in blood loss between the mild hypothermia (916.8±430.5) and moderate hypothermia (1082.3±502.03) group, with a p-value = 0.176. There were no significant differences in inotropic support measures, including dopamine infusion rate (p = 0.618) and nor-adrenaline infusion rate (p = 0.209). However, the adrenaline infusion rate (p = 0.001) was significantly different between the mild hypothermia [0.05 (0.06-0.04)] and moderate hypothermia [(0.04 (0.04-0.03))] group with the mild hypothermia group exhibiting a slightly higher dosage of adrenaline infusion. Additionally, the hours of ventilation did not differ significantly between the mild [177.5 (140-217.5)] and moderate hypothermia [160 (138.7-306.2)] groups,

**Table 3:** Intraoperative and Postoperative Patient Variables

Parameter	Types of Hypothermia		p-value
	Moderate (n=30)	Mild (n=30)	
<b>Intraoperative Phase</b>			
CPB time (minutes)	132 (110-157.7)	114 (91.2-137.5)	0.017
ACC (minutes)	78 (62.5-94.7)	62 (54-73.2)	0.005
Hb (g/dL)	8.8 (7.7-10.1)	7.85 (7.3-8.7)	0.025
<b>Postoperative Phase</b>			
Hb (g/dL)	9.59 (8.89-10.7)	9.75 (8.62-11.2)	0.717
TLC (10 <sup>3</sup> /μL)	13.3 (10.7-17.5)	13.2 (10.7-15.2)	0.620
PLT (10 <sup>3</sup> /μL)	180.65 (156-198.6)	172(145.5-245.9)	0.871
SGPT (U/L)	28 (23.9-39.5)	25.05 (17.4-34.3)	0.160
SGOT (U/L))	48.2 (27.6-71.1)	30.4 (30-48.1)	0.363
Blood urea (mg/dL)	34.7 (27.4-44.2)	27.3 (24.9-37.6)	0.058
Serum creatinine (mg/dL)	0.96 (0.84-1.2)	0.90 (0.81-1.07)	0.219
Blood transfusion; n(%)	18 (60)	21 (70)	0.417
Amount of blood loss (mL)	1082.3±502.03	916.8±430.5	0.176
Ventilation time (minutes)	160 (138.7-306.2)	177.5 (140-217.5)	0.762
Adrenaline infusion rate (mcg/kg/min)	0.04 (0.04-0.03)	0.05 (0.06-0.04)	0.001
Nor adrenaline infusion rate (mcg/kg/min)	0.05±0.01	0.05±0.02	0.209
Dopamine infusion rate (mcg/kg/min)	4 (4-2)	2 (4-2)	0.618
ICU stay (days)	7 (6-8)	6 (5-7)	0.045
Mortality; n (%)	0 (0.00)	0 (0.00)	0.000
Postoperative MMSE score	22.8±2.90	23.1±4.009	0.687

with a p-value of 0.762. Although a statistically significant difference was observed in ICU length of stay (p = 0.045), with longer stays in the moderate hypothermia group, the corresponding 95% confidence interval suggested a modest effect size, and this finding should therefore be interpreted cautiously. (Table 3).

Hb levels during CPB were found to be significant (p = 0.025) between the mild [7.85 (7.3-8.7)] and moderate hypothermia [8.8 (7.7-10.1)] group, with the latter group exhibiting slightly higher Hb levels. A p-value of 0.017 was found for the CPB time, with longer CPB time experienced by the moderate hypothermia group

[132 (110-157.7)] as compared to the mild hypothermia group [114 (91.2-137.5)]. Similarly, a significant difference was found for the ACC time ( $p = 0.005$ ), with the moderate hypothermia group (62 [54-73.2]) having a longer ACC time compared to the mild hypothermia group (62 [54-73.2]). However, other postoperative parameters, including the Complete Blood Count (CBC), had no significant differences in Hb levels ( $p = 0.717$ ), platelet count (PLT) ( $p = 0.871$ ), and total leukocyte count (TLC) ( $p = 0.620$ ) between the two groups. Additionally, the creatinine ( $p = 0.219$ ) and urea levels ( $p = 0.058$ ) came out to be insignificant, along with the SGPT ( $p = 0.160$ ) and SGOT ( $p = 0.363$ ) levels. The lack of significant differences indicates that these outcomes are not markedly affected by the degree of hypothermia. (Table 3)

## Discussion

The use of hypothermia during cardiopulmonary bypass is now routine, as it has been shown to provide organ protection and several physiological benefits.<sup>12</sup> However, hypothermia is also associated with potential adverse effects, and due to its diverse physiological impact, the optimal temperature management strategy during CPB remains a subject of debate.<sup>13</sup> Experimental and clinical data suggest that for every one-degree reduction in temperature, blood loss may increase by approximately 16%, highlighting one of the potential drawbacks of hypothermic techniques.<sup>16</sup> Neurocognitive dysfunction is another recognized complication that has been variably associated with hypothermia during CPB.<sup>11</sup>

In the present study, no statistically significant difference was observed in postoperative neurocognitive outcomes between patients undergoing mild versus moderate hypothermia, as assessed by postoperative MMSE scores. These findings are consistent with several published studies demonstrating that temperature ranges within mild-to-moderate hypothermia do not significantly influence the incidence of postoperative cognitive dysfunction.<sup>17</sup> A systematic review and meta-analysis by Linassi et al. reported no clear association between CPB temperature and postoperative neurocognitive impairment, supporting the results of the current investigation<sup>(11)</sup>. Similar conclusions have been drawn by other studies suggesting that moderate hypothermia does not increase the risk of embolic events or stroke-related cognitive deficits.<sup>18</sup> The optimal CPB temperature for preventing neurocognitive issues remains unclear, but moderate hypothermia does not increase the risk of emboli or stroke-related cognitive problems.<sup>19,20</sup> In terms of secondary outcomes, no significant difference was observed in the duration of mechanical venti-

lation between the two hypothermia groups, a finding consistent with previous work by Bianco et al.<sup>21</sup>

Similarly, blood loss did not differ significantly between groups, although earlier studies have reported conflicting results regarding the relationship between hypothermia and perioperative bleeding.<sup>4</sup>

A statistically significant difference was observed in the length of ICU stay, with patients in the moderate hypothermia group demonstrating a longer duration of ICU admission compared to those in the mild hypothermia group. This finding contrasts with reports by Bianco et al., who documented longer ICU stays in mildly hypothermic patients, underscoring the variability of clinical outcomes reported in the literature and the influence of institutional practices.<sup>21</sup>

Inotropic support requirements serve as indirect markers of postoperative hemodynamic stability and potential complications. In the present study, adrenaline infusion rates were significantly higher in the mild hypothermia group, a finding that aligns with previous reports suggesting differential inotropic requirements based on temperature management strategies.<sup>22,23</sup> Dopamine and noradrenaline requirements, however, did not differ significantly between groups.

The longer cardiopulmonary bypass and aortic cross-clamp times observed in the moderate hypothermia group may be attributed to the additional cooling and rewarming phases inherent to deeper hypothermic strategies, which can prolong operative duration.<sup>4</sup>

Despite these differences, no significant impact was observed on postoperative biochemical parameters, renal function, or hematological indices. Overall, efforts were made to maintain a homogeneous study population to minimize confounding variables. The findings of this study are consistent with recent meta-analyses and contribute to the growing body of evidence suggesting that mild and moderate hypothermia during CPB yield comparable neurocognitive outcomes. Therefore, the choice of hypothermic strategy should be individualized, weighing potential benefits against associated risks.

## Conclusion

Our study found no significant difference in postoperative neurocognitive function between mild and moderate hypothermia during CPB. Secondary outcomes, including ventilation duration, blood loss, and dopamine/noradrenaline support, showed no significant variation. However, ICU stay and adrenaline infusion rates differed,

suggesting recovery may vary based on the degree of hypothermia received.

### Limitations:

The relatively small sample size limits the generalizability of the findings and may reduce the ability to detect smaller but clinically meaningful differences between groups. Although random allocation was employed, the data analysis did not adjust for potential confounding variables such as baseline biochemical differences, type of surgical procedure, cardiopulmonary bypass duration, and aortic cross-clamp time. The absence of multivariable or regression-based analyses limits the ability to determine the independent effect of hypothermia on neurocognitive and secondary outcomes. In addition, postoperative neurocognitive assessment was confined to the early postoperative period and relied on a single screening tool, which may not capture subtle or delayed cognitive changes. Future studies incorporating larger cohorts, longer follow-up, and adjusted multivariate analyses are warranted.

**Ethical Approval:** The Institutional Review Board, KEMU approved this study vide No.129/RC/KEMU.

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### Authors' Contribution:

**IA:** Conception & design, acquisition of data, drafting of article

**AH:** Acquisition of data, drafting of article, analysis & interpretation of data, final approval of the version to be published

**IAK:** Critical revisions for important intellectual content, final approval of the version to be published

**MA:** Conception & design, acquisition of data

**SN:** Acquisition of data

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