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## Research Article

### Hypothermic Circulatory Arrest Is Associated with Increased Risk of Postoperative Delirium: A Retrospective Cohort Study

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#### Abstract

**Objectives:** This study aimed to measure the incidence of postoperative delirium (POD) after aortic arch surgery with hypothermic circulatory arrest (HCA), compare it to cardiac surgeries not requiring HCA, and investigate whether neuroprotection subgroups displayed different incidences.

**Design:** Retrospective cohort study

**Setting:** Single academic medical center

**Participants:** Patients over 18 years old undergoing cardiovascular surgery between July 2020 and May 2022, requiring cardiopulmonary bypass with HCA (n = 165) or without HCA (n = 1974).

**Interventions:** HCA with various neuroprotection strategies including deep hypothermia (DHCA, 14.1°C - 20°C), moderate hypothermia (MHCA, 20.1 - 28°C), no cerebral perfusion (NCP), antegrade cerebral perfusion (ACP), or retrograde cerebral perfusion (RCP).

**Measurements and Main Results:** POD was assessed on postoperative days one through five, using the Confusion Assessment Method. POD occurred in 51 (30.9%) patients in the HCA group and 225 (11.4%) patients in the non-HCA group (odds ratio 1.93; 95% CI: 1.24-2.97, p=0.003). Patients who underwent DHCA had a higher incidence of POD than those who underwent MHCA (40.2% vs. 16.7%, p = 0.001). There was no statistically significant difference in the incidence of POD between patients in the NCP, ACP and RCP subgroups.

**Conclusions:** Postoperative delirium is more common following aortic arch surgery with HCA, particularly DHCA, compared with non-aortic arch surgery. Aortic arch surgery with HCA is associated with higher incidence of cardiopulmonary and renal complications. Additional studies are needed to identify interventions that improve postoperative neurocognitive outcomes in this high-risk patient population.

**Keywords:** Delirium, Cardiac Surgery, Aortic Arch Surgery, Hypothermic Circulatory Arrest, Postoperative, Neurocognition, neurocognitive disorder, cerebral perfusion

## Introduction

Postoperative delirium (POD) is the most common neurologic complication in patients undergoing cardiac surgery and the incidence ranges from 4% to 55% depending on the patient population, surgery type, and duration of cardiopulmonary bypass [1,2]. POD is associated with increased mortality, extended hospital stays, long-term cognitive decline and financial burden for families and healthcare systems [1,3,4]. The mechanism for POD is complex and likely multifactorial, including ischemia-related cerebral injury [5–7] and systemic contributors such as inflammation and multiorgan failure [8]. Patients undergoing aortic arch surgery requiring hypothermic circulatory arrest (HCA) are among those with the highest mortality and risk of postoperative neurological complications [9,10]. However, POD following aortic arch surgery is poorly studied due to inconsistent nomenclature and screening tools to diagnose postoperative neurological complications after these surgeries, and the unique confounders of variable neuroprotection strategies during HCA [9–11]. For example, the definition of temporary neurologic deficit originally described by Ergin etc. has been largely replaced with postoperative delirium [2,11]. Therefore, the reported incidence of POD in patients after aortic arch surgery varies widely, with temporary neurologic dysfunction and delirium often being used interchangeably [12–15]. Studies that systematically compare POD between HCA and non-HCA cardiovascular surgeries using consistent terminology and screening tools are needed to better define this common complication.

Much of the effort in aortic arch surgery has focused on neuroprotection during circulatory arrest to avoid neurologic complications [10,16]. While deep hypothermic circulatory arrest (DHCA) with no cerebral perfusion (NCP) is still the most common technique for neuroprotection in many institutions, retrograde cerebral perfusion (RCP) has been deployed as an adjunct to DHCA, and antegrade cerebral perfusion (ACP) has gained popularity in patients requiring prolonged circulatory arrest or a lesser degree of hypothermia [17,18]. By providing cold blood via the carotid arterial system, ACP regulates cerebral temperature and delivers metabolic substrates to neurons during circulatory arrest. Conversely, RCP via the superior venous system flushes out possible emboli from the cerebral circulation and provides additional cooling of the brain [19]. Despite these innovations in cerebral protection, even DHCA combined with ACP is associated with grey matter loss and impaired functional connectivity, highlighting the inherent challenges in developing neuroprotection strategies in this vulnerable patient population [20]. Furthermore, the correlation between cerebral protection strategy (temperature and selective cerebral perfusion), and POD is still largely unknown.

This retrospective study aims to examine the incidence of POD following aortic arch surgery with HCA in a major teach-

ing institution. We hypothesized that patients undergoing aortic arch surgery with HCA would have a higher incidence of POD compared to patients undergoing cardiac surgery without HCA. We also hypothesized that the rate of POD would differ between neuroprotection subgroups, namely temperature (DHCA, MHCA) and selective cerebral perfusion strategies (ACP, RCP, NCP). The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21].

## Methods

### Participants

This retrospective cohort study included patients aged 18 years and older who underwent cardiac surgery requiring cardiopulmonary bypass (CPB) from July 2020 to May 2022 at Massachusetts General Hospital (MGH), a large urban tertiary care teaching hospital in Boston, MA, USA. Patients who underwent HCA for non-aortic arch surgery (pulmonary thromboendarterectomy) that have very different pathophysiology were excluded. Perioperative data including demographic information, clinical history, laboratory findings, and postoperative outcomes were retrieved from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) [22]. We followed STS guideline on cooling and rewarming for patients undergoing cardiac surgery including those required hypothermic circulatory arrest. No pharmacological intervention was delivered by the anesthesiologists or perfusionists before HCA. The Mass General Brigham Institutional Review Board approved this study with a waiver of informed consent before the implementation of any study procedures.

Postoperative delirium, defined as any occurrence of delirium on postoperative day one through day five, was queried from nursing assessments in the electronic medical record using the confusion assessment method, as previously described [23]. Each patient was assessed at least twice daily in morning and afternoon, with at least 6 h separating assessments, for five days or until the patient was discharged from the hospital. POD was recorded as a binary variable (yes/no). Patients were considered delirious if they had any positive CAM documented during the above defined postoperative period. Other postoperative outcomes include intensive care unit (ICU) length of stay, hospital length of stay, re-exploration rate for bleeding, incidence of stroke and encephalopathy, prolonged mechanical ventilation requirements, pneumonia incidence, renal failure incidence, atrial fibrillation incidence, and 30-day mortality.

### Power Analysis

There was no a priori power analysis performed to guide sample size determination. A convenience sampling meth-

od was used to utilize all available study data reflecting real-world contemporary clinical practice between July 2020 to May 2022.

### Statistical Analysis

Descriptive statistics are presented as means and standard deviations (SD) or medians and 25th /75th percentiles for continuous variables depending on the specific data distributions. Normality was assumed based on the central limit theorem. Categorical variables were summarized as frequencies and relative percentages. We compared the differences between groups of those who developed versus who did not develop postoperative delirium. Two-independent-sample t-tests or its non-parametric equivalence of Wilcoxon tests, Chi-square tests or Fisher's Exact tests were performed for inferences based on their variable types and distributions, respectively.

Multivariable Logistic regression was employed to assess the association between HCA status and postoperative delirium. We included confounding variables of age, gender, history of lung disease, diabetes, history of stroke, surgical status (elective, urgent, emergency), circulatory arrest time, cardiopulmonary bypass time and aortic cross-clamp time for adjustments. The Multiple imputations (MI) method was used to impute missing data for postoperative delirium. Specifically, we utilized multiple imputations by chained equations (MICE), with  $m = 10$  iterations, following a sequential regression approach. Imputed logistic regression outputs were subsequently pooled based on Rubin's rules. Variables used for MICE imputation included age, gender, body mass index (BMI), past medical history, cardiac pathology, preoperative laboratory values, surgery status (elective, urgent, emergency), redo sternotomy, type of surgery, intraoperative factors (nadir temperature, cardiopulmonary bypass time, circulatory arrest time, cerebral perfusion type and duration, blood transfusion), and postoperative factors (ICU and hospital length of stay, postoperative laboratory values, and other complications).

All analyses are two-tailed and an alpha level of 0.05 was used to declare significance where Bonferroni correction [24] was used to account for multiple comparisons when appropriate. Analysis was performed using the latest version of R statistical software (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (Posit PBC, Boston, MA).

## Results

### Preoperative and surgical Characteristics

Between July 2020 to May 2022, a total of 2,167 patients aged 18 years and older underwent cardiac surgery requiring cardiopulmonary bypass (Figure 1). Complete CAM documentation was recorded in 1,896 patients, which was increased to 2,139 patients following multiple imputation and excluding patients who underwent HCA for non-aortic arch

surgery (28 patients). Of these, 165 (7.7%) patients had aortic arch surgery requiring HCA (CA group). Overall, gender was balanced in both groups, and patients were younger in the CA group. Compared to the NCA group, patients in the CA group had a lower incidence of diabetes mellitus (14.5% vs. 29.1%,  $p < 0.001$ ), prior myocardial infarction (10.3% vs. 25.2%,  $p < 0.001$ ), and heart failure (33.9% vs. 44.4%,  $p = 0.009$ ), and were more likely to have peripheral arterial disease (20.6% vs. 13.7%,  $p = 0.015$ ) (Table 1).

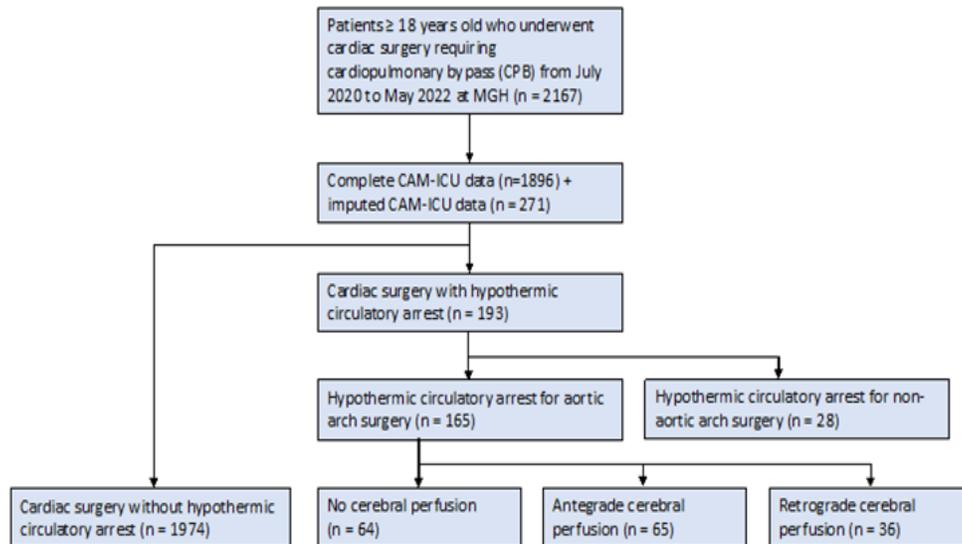
Compared to the NCA group, patients in the CA group had a significantly higher proportion of emergency surgery (24.8% vs. 2.7%,  $p < 0.001$ ) and redo sternotomy (29.7% vs. 15.1%,  $p < 0.001$ ), longer cross clamp and cardiopulmonary bypass times ( $167 \pm 74.0$  vs.  $112 \pm 62.0$  min,  $p < 0.001$ ;  $242 \pm 72.4$  vs.  $149.0 \pm 68.9$  minutes,  $p < 0.001$ , respectively) (Table 2). Details of neuroprotection strategies are presented in Table 3. In total, 104 (63%) patients underwent DHCA (14 - 20°C), 59 (36%) patients underwent moderate HCA (MHCA, 20.1 - 28°C), and 2 (1%) patients underwent mild HCA (28.1 - 34°C). Sixty-four (39.4%) patients received ACP, 36 (21.8%) received RCP, and 64 (38.8%) did not have any cerebral perfusion. The circulatory arrest times for 26 moderate hypothermic patients without ACP were all under 18 minutes and the patient with mild hypothermia had a circulatory arrest time  $< 10$  minutes.

### Postoperative Delirium and Other Outcomes

The Multiple imputations (MI) replaced missing data for postoperative delirium in 302 patients on postoperative day one, 195 patients on postoperative day two, 161 patients on postoperative day three, 150 patients on postoperative day four, and 124 patients on postoperative day five. Table 4 reports postoperative outcomes for patients in both the CA and NCA groups. Postoperative delirium occurred in a total of 276 patients (12.9%) and was significantly higher in the CA group (30.9% vs 11.4%,  $p < 0.001$ ). After adjusting for confounding variables, the association between aortic arch surgery with HCA and POD remained significant (OR 1.93; 95% CI, 1.24 to 2.97;  $P = 0.003$ ).

The incidence of POD was significantly higher ( $p = 0.001$ ) in patients who underwent DHCA (40.2%) compared to those who underwent MHCA (16.7%). The incidence of POD did not differ significantly between patients who underwent ACP (36.9%), RCP (36.1%), or no cerebral perfusion (21.9%) during circulatory arrest ( $p = 0.135$ ).

For other postoperative outcomes, patients in the CA group had longer ICU length of stay and hospital length of stay, as well as a higher risk of postoperative stroke, prolonged ventilator use, pneumonia, renal failure, and atrial fibrillation (Table 4). The risk of sternal infection and reoperation, as well as 30-day mortality, were similar between patients who underwent HCA and those who did not.



**Figure 1:** Flow chart of patients included in the study. MGH, Massachusetts General Hospital; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit.

	All patients (N=2139)	Hypothermic circulatory arrest		p value
		No (N=1974)	Yes (N=165)	
<b>Patient age</b>	63 (12.8)	63 (12.7)	61 (13.8)	0.018
<b>Female</b>	600 (28.1)	556 (28.2)	44 (26.7)	0.680
<b>BMI</b>	28.4 (5.9)	28.3 (5.8)	29.0 (6.3)	0.184
<b>Diabetes</b>	598 (28.0)	574 (29.1)	24 (14.5)	< 0.001
<b>Prior MI</b>	515 (24.1)	498 (25.2)	17 (10.3)	< 0.001
<b>Heart failure</b>	933 (43.6)	877 (44.4)	56 (33.9)	0.009
<b>Preoperative atrial fibrillation</b>	501 (23.4)	466 (23.6)	35 (21.2)	0.485
<b>Dialysis</b>	57 (2.7)	53 (2.7)	4 (2.4)	0.842
<b>Hypertension</b>	1620 (75.7)	1492 (75.6)	128 (77.6)	0.566
<b>Smoker</b>	1043 (48.8)	956 (48.4)	87 (52.7)	0.289
<b>Lung disease</b>	340 (15.9)	312 (15.8)	28 (17.0)	0.694
<b>Peripheral arterial disease</b>	305 (14.3)	271 (13.7)	34 (20.6)	0.015
<b>Prior stroke</b>	237 (11.1)	217 (11.0)	20 (12.1)	0.657
<b>Preoperative hemoglobin</b>	13.2 (2.2)	13.2 (2.2)	13.1 (2.2)	0.764
<b>Preoperative creatinine</b>	1.1 (0.8)	1.1 (0.7)	1.2 (1.2)	0.531
<b>Preoperative albumin</b>	4.2 (0.6)	4.2 (0.6)	4.1 (0.6)	0.099
<b>Preoperative INR</b>	1.1 (0.3)	1.1 (0.3)	1.2 (0.5)	< 0.001

Values for continuous variables are expressed as mean ± standard deviation. Values for categorical variables are expressed as numbers (%). BMI, body mass index; MI, myocardial infarction; INR, international normalized ratio.

**Table 1:** Preoperative patient characteristics and lab values for non-circulatory arrest and circulatory arrest groups

	All patients (N=2139)	Hypothermic circulatory arrest		p value
		No (N=1974)	Yes (N=165)	
<b>Surgical status</b>				< 0.001
Elective	1263 (59.0)	1173 (59.4)	90 (54.5)	
Emergent	94 (4.4)	53 (2.7)	41 (24.8)	
Urgent	782 (36.6)	748 (37.9)	34 (20.6)	
<b>Redo sternotomy</b>	347 (16.2)	298 (15.1)	49 (29.7)	< 0.001
<b>Nadir temperature</b>	31.9 (4.2)	32.9 (2.3)	20.0 (3.0)	< 0.001
<b>Cardiopulmonary bypass time (min)</b>	156 (73.6)	149 (68.9)	242 (72.4)	< 0.001
<b>Cross clamp time (min)</b>	117 (64.7)	112 (62)	167 (74.0)	< 0.001

Values for categorical variables are expressed as numbers (%).

**Table 2:** Surgical characteristics for non-circulatory arrest and circulatory arrest groups.

	All hypothermic circulatory arrest (n=165)	Deep hypothermic circulatory arrest (n=104)	Moderate hypothermic circulatory arrest (n=59)	Mild hypothermic circulatory arrest (n=2)
<b>Circulatory arrest time (min)</b>	36.4 (29.4)	40.2 (32.3)	30.4 (22.4)	10.5 (13.4)
<b>Cerebral perfusion</b>				
Antegrade	65 (39.4)	37 (35.6)	27 (45.8)	1 (50)
Retrograde	36 (21.8)	30 (28.9)	6 (10.2)	-
None	64 (38.8)	37 (35.6)	26 (44)	1 (50)

Values for continuous variables are expressed as mean  $\pm$  standard deviation. Values for categorical variables are expressed as numbers (%).

**Table 3:** Circulatory arrest time and cerebral perfusion type in hypothermic circulatory arrest groups.

	All patients (N=2139)	Hypothermic circulatory arrest		p value
		No (N=1974)	Yes (N=165)	
<b>Postop delirium</b>	276 (12.9)	225 (11.4)	51 (30.9)	< 0.001
<b>ICU length of stay</b>	87 (160.9)	82 (151.7)	146 (238.3)	< 0.001
<b>Hospital length of stay</b>	10 (12.0)	10 (10.5)	15 (22.5)	< 0.001
<b>Sternal wound infection</b>	25 (1.2)	23 (1.2)	2 (1.2)	0.957
<b>Bleeding requiring reoperation</b>	66 (3.1)	58 (2.9)	8 (4.8)	0.173
<b>Stroke</b>	46 (2.2)	33 (1.7)	13 (7.9)	< 0.001
<b>Encephalopathy</b>	15 (0.7)	12 (0.6)	3 (1.8)	0.073
<b>Prolonged ventilation</b>	309 (14.4)	256 (13.0)	53 (32.1)	< 0.001
<b>Pneumonia</b>	118 (5.5)	99 (5.0)	19 (11.5)	< 0.001
<b>Renal failure</b>	79 (3.7)	65 (3.3)	14 (8.5)	< 0.001
<b>Postoperative atrial fibrillation</b>	714 (33.4)	645 (32.7)	69 (41.8)	0.017
<b>30-day mortality</b>	42 (2.0)	36 (1.8)	6 (3.6)	0.111

Values for continuous variables are expressed as mean  $\pm$  standard deviation. Values for categorical variables are expressed as numbers (%). ICU, intensive care unit.

**Table 4:** Postoperative characteristics for non-circulatory arrest and circulatory arrest groups.

## Discussion

In this large, single-center, retrospective cohort study, we show that POD was more common after surgeries requiring HCA than those not requiring HCA, that DHCA was associated with a higher rate of POD than MHCA, and that selective cerebral perfusion strategies did not have a significant impact on the incidence of POD.

The incidence of POD in patients undergoing non-aortic arch surgery in our study (12.9%) is consistent with the incidence reported in The Minimizing ICU Neurological Dysfunction with Dexmedetomidine induced Sleep (MINDDS) trial, conducted at the same institution [23,25,26].

To date there has been no direct comparison of the incidence of POD between patients who underwent cardiac surgery without HCA to those who underwent aortic surgery with HCA. After correcting for major confounders including cardiopulmonary bypass and cross-clamp times, patients who underwent aortic arch surgery requiring HCA at our institution still had an almost two-fold risk of developing POD compared to those who underwent cardiac surgery without HCA. The incidence of POD in patients who underwent HCA in our study (30.9%) is comparable to studies of patients following aortic dissection repair [2,27]. Our finding that the incidence of POD did not differ between cerebral perfusion subgroups suggests that the mechanisms for POD are different from those of stroke, and therefore may be amenable to alternative mitigation strategies [13,28,29].

Most clinical trials studying POD in cardiac surgery exclude patients undergoing aortic arch surgery requiring HCA because of the increased risk of cerebral injury [23,30]. However, delirium and cognitive dysfunction are the most common neurologic complications in cardiac surgery [9,11,13]. Neurologic complications after aortic arch surgery are currently classified into permanent and temporary neurologic dysfunction, defined in 1993 [11]. Many studies do not report the screening tools used to diagnose neurologic dysfunction, or still use the definition of temporary neurologic dysfunction for delirium in patients undergoing aortic arch surgery [13,31,32]. Furthermore, POD has not officially been listed as a neurologic outcome in STS database, limiting large-scale, multicenter, retrospective studies [33].

DHCA is still the dominant cerebral protection technique for aortic arch surgery in many institutions, and accounted for 66% of HCA cases in our dataset [34]. A recent multicenter randomized clinical trial found that when combined with ACP, low MHCA (20.1 – 24 °C) was non-inferior to DHCA ( $\leq 20^{\circ}\text{C}$ ) for a primary outcome of global cognitive change four weeks postoperatively [20]. However, all patients who underwent HCA showed significant cortical thickness loss and reduced functional connectivity, which correlated with impaired structured verbal memory and attention, respectively. These findings point to the fact that HCA, even when combined with ACP, causes neurological harm. The relationship of HCA,

temperature and POD is less well defined. A retrospective study of 72 patients undergoing aortic arch reconstruction by Cook et al. failed to find a significant difference in the incidence of postoperative delirium between patients who underwent ACP with HCA  $> 22^{\circ}\text{C}$ , versus ACP with HCA  $< 22^{\circ}\text{C}$  (10.0% delirium rates with HCA  $> 22^{\circ}\text{C}$  vs. 30.8% with HCA  $< 22^{\circ}\text{C}$ ,  $p=0.07$ ) [35]. The reported trend towards a higher incidence of POD in patients with HCA  $< 22^{\circ}\text{C}$  suggests that their sample size may have been too small to confirm a statistically significant difference. In contrast, our larger study (165 patients undergoing HCA) did find a statistically significant increase in the incidence of POD for patients who underwent DHCA compared to MHCA (40.2% vs. 16.7%,  $p = 0.001$ ). These results expand the body of evidence associating the target temperature during HCA with delirium and should be confirmed in future prospective studies.

More than half of the patients in our study underwent aortic arch surgery using supplemental brain protection with RCP or ACP. This is consistent with the trend in aortic arch surgery for neuroprotection. There are an increasing number of patients undergoing aortic arch surgery with moderate or even mild hypothermia supplemented with ACP. Circulatory arrest time is also an important factor as showed in this study. Moderate or even mild hypothermia with short circulatory arrest is also safe in some patients without supplemental cerebral perfusion [10]. The optimal cerebral perfusion and neuro-monitoring techniques during HCA remain controversial and evolving. For example, although ACP provides metabolic substrates to neurons during HCA, macro- and micro-emboli from ACP could potentially increase silent brain infarctions and increase the risk of POD [7,36]. In our study, there was a trend towards a higher incidence of POD in patients receiving ACP and RCP compared to no cerebral perfusion; however, this difference was not statistically significant.

Our study has notable strengths compared to previous investigations of POD after aortic arch surgery. First, our definition of POD leverages a validated screening tool (CAM) and is aligned with recommended nomenclature for perioperative neurocognitive disorders [37,38]. Furthermore, our moderately large sample size reflects the high volume of these surgeries at our center, and enabled us to control for a substantial number of known confounding variables for POD. Our sample also included variability in targeted HCA temperatures and selective cerebral perfusion strategies, which allowed us to perform subgroup analyses that can be used to inform future prospective trials.

This study also has limitations worth considering. First, due to its retrospective nature, there was no reliable baseline cognitive function assessment or randomization across neuroprotection groups. We also used multiple imputation to account for missing delirium data. Residual confounding may also affect our results. Therefore, these findings should be con-

firmed in prospective trials. Second, this was a single-center study using a convenience sample, conducted at a tertiary care center, and therefore may not generalize across a more heterogeneous patient population. Third, although the incidence of POD extracted from nursing documentation in our study was similar to another prospective study conducted at our institution where POD assessment was performed by dedicated research staff, retrospective chart review and intermittent screening tools both carry the risk of misdiagnosing POD, particularly the hypoactive subtype. Recent studies suggest that continuous electroencephalography (EEG) may be a helpful tool to diagnose and track delirium severity throughout the postoperative period, supplementing traditional screening tools like CAM-ICU which are limited by low temporal resolution and inter-operator variability [39–41]. Future studies investigating POD after aortic arch surgery should consider including perioperative EEG analyses to identify pre-, intra- and postoperative biomarkers specific to this high-risk patient population.

## Conclusions

Postoperative delirium is a common neurologic complication following cardiac surgery. Aortic arch surgery requiring hypothermic circulatory arrest is associated with higher risk of postoperative delirium and poor cardiopulmonary and renal outcomes compared to non-aortic arch surgery. As optimal cerebral protection strategy evolves, prospective, multicenter trials will help uncover the optimal neuroprotection strategies that minimize postoperative delirium after hypothermic circulatory arrest, particularly selective cerebral perfusion strategies and temperature management. An updated definition and diagnostic tools of neurologic outcomes is needed for patients undergoing aortic arch surgery requiring hypothermic circulatory arrest [13,37].

## Declarations

**Running Head:** Postoperative delirium after aortic arch surgery and hypothermic circulatory arrest

**Competing interests statement:** The authors declare no competing interests.

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### Author Contributions:

Conceptualization: AL, JZQ

Data Curation: AL, TH, AM, JZQ, CSG

Formal Analysis: AL, TH, AM, CSG

Methodology: AL, TH, AM, CSG

Investigation: AL, DH, HD, AM, AAW, TH, JZQ, CSG

Project administration: JZQ, TS, CSG

Supervision: JZQ, TS, CSG

Writing: AL, DH, HD, AM, AAW, TH, JZQ, CSG

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