

# Cardiopulmonary Bypass Mean Global Oxygen Delivery May Be Associated with Neurocognitive Preservation during Hypothermic Aortic Surgery

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**Abstract:** The purpose of this retrospective research was to investigate the relationship between mean global oxygen delivery ( $\text{DO}_2$ ) and neurocognitive function in adult patients who presented for aortic surgery with deep hypothermic circulatory arrest using cardiopulmonary bypass (CPB). From a pool of 132 patients, data from 100 CPB patients from 2012 to 2014 aged 50 years or older were randomly selected and analyzed, and global  $\text{DO}_2$  on CPB was used to categorize patients into those for whom the mean indexed cerebral oxygen delivery ( $\text{DO}_{2i}$ ) was either  $\geq 272 \text{ mL O}_2/\text{min}/\text{m}^2$  (critical  $\text{DO}_2$  [ $\text{DO}_{2\text{crit}}$ ]) or less than  $\text{DO}_{2\text{crit}}$ . Ten patients experienced either stroke or expired in the perioperative course. The proportion of patients with evidence of neurocognitive preservation was 98.3% in the group in which the

$\text{DO}_{2\text{crit}}$  was met, compared with 80.6% in the group where  $\text{DO}_{2\text{crit}}$  was not met ( $\chi^2 [1, 100] = 3.27, p = .07$ ). Potentially, because of causes other than  $\text{DO}_2$ , the subset of patients with stroke and/or death were removed, and data from 90 cases were analyzed, and a global mean  $\text{DO}_{2i}$  value of  $239.9 \text{ mL O}_2/\text{min}/\text{m}^2$  was identified. A larger sample size with controls may yield deeper insights into the hypothesis that a mean global CPB  $\text{DO}_{2i}$  of  $239.9 \text{ mL O}_2/\text{min}/\text{m}^2$  may play a role in predicting neurocognitive preservation in this patient population. **Keywords:** acute kidney injury (AKI), cardiopulmonary bypass (CPB), cerebral performance category (CPC), neurocognitive preservation/loss, critical oxygen delivery ( $\text{DO}_{2\text{crit}}$ ), modified Rankin Scale (mRS). *J Extra Corpor Technol. 2020;52:289–94*

The fact that multiple and, sometimes, mixed mechanisms may contribute to post-cardiac surgery neurocognitive dysfunction is well established, with comorbidities and iatrogenic factors both playing causative roles (1). A few of the reported comorbidities include advanced age, pre-existing vascular and cerebrovascular disease, the presence of preoperative ischemic lesions, and low baseline assessment of neuropsychological performance and/or preoperative impairment (2–4).

Three of the most commonly reported iatrogenic factors are cerebrovascular embolism (solid or gaseous), inflammation, and low oxygen delivery ( $\text{DO}_2$ ) secondary to hypoperfusion, all of which may result in regional cerebral

ischemia (2,5). In addition, the systemic inflammatory response associated with foreign surface contact of the cardiopulmonary bypass (CPB) circuit, atherosclerotic plaques being dislodged during cannulation of the aorta, hyper-perfusion, diminished  $\text{DO}_2$  secondary to hypoperfusion, and the re-warming process associated with hypothermic CPB have all been noted to include abnormal cerebral blood flow, potentially leading to ischemic cerebral conditions (5,6).

Several reports have focused on the importance of reducing the overall incidence of cerebrovascular embolisms to diminish the incidence of neurocognitive dysfunction (7–10). Other investigators have focused on the role of inflammation in post-cardiac surgery cognitive dysfunction (11,12). However, low  $\text{DO}_2$  and the concept referred to as critical  $\text{DO}_2$  have yet to be explored in this population of patients.

$\text{DO}_{2\text{crit}}$  is referred to as the boundary of shock, delineating the region of physiologic response between regional or global aerobic and anaerobic metabolism. Although

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much has been and is currently being learned in the laboratory environment regarding tissue  $\text{DO}_2$  and the fluctuations that occur in the small and microvasculature in striated muscle (13), assumptions remain regarding the delivery of oxygen-related mechanisms in specific organs, such as the brain and kidneys.

Under conditions of normal autoregulation, the kidneys receive approximately 20% of the resting cardiac output, with the brain receiving approximately 15% (14,15). And while using approximately one-fifth of all circulating oxygen, normal cerebral  $\text{O}_2$  consumption (cerebral volume of oxygen consumption [ $\text{VO}_2$ ]) is approximately 3.5 mL/100 g brain tissue/min, meaning that the average brain with a mass of approximately 1,400 g has a basal metabolic rate of approximately 49 mL  $\text{O}_2$   $\text{min}^{-1}$  (15).

However, the normal autoregulatory process guiding global blood flow may be interrupted during CPB, introducing the potential for diminished  $\text{DO}_2$  through hypoperfusion, potentially leading to ischemia (16). In addition, the patient mean arterial pressure range and limits that are associated with cerebral autoregulation while on CPB are unique (17) and are unlikely to be maintained during the entire process of inducing and reversing global hypothermia.

Global CPB  $\text{DO}_{2i}$  has been investigated to reduce the incidence of acute kidney injury (AKI), and both a nadir of  $272 \text{ mL} \times \text{min}^{-1} \times \text{m}^{-2}$  and time-dose response of  $<300 \text{ mL} \times \text{min}^{-1} \times \text{m}^{-2}$  for  $\leq 15$  minutes have been shown to be effective (18,19). However, during hypothermic CPB with circulatory arrest,  $\text{DO}_{2i}$  values can fluctuate and are frequently adjusted to account for both the Pasteur effect and decreased metabolic demand, making nadir and time-dose response values clinically challenging to acquire. However, mean  $\text{DO}_{2i}$  values taken from the entire course of CPB can be acquired and compared with the lower of the two AKI threshold values (nadir of  $272 \text{ mL} \times \text{min}^{-1} \times \text{m}^{-2}$ ) to evaluate the relationship between global CPB  $\text{DO}_{2i}$  and the preservation of neurocognition. Knowing that cerebral tissue ischemia and hypoxia can result in neurodegeneration, which can then lead to either acute neuronal cell death or a delayed, apoptotic neuronal cell death (20), a study was conducted to examine the relationship between mean global CPB  $\text{DO}_2$  at or above  $\text{DO}_{2\text{crit}}$  and neurocognitive preservation in patients undergoing hypothermic aortic surgery.

## MATERIALS AND METHODS

Following Mayo Clinic IRB approval (November 30, 2016, #16-009557), 100 patients aged 50 years or older who had elective aortic surgery using CPB between 2012 and 2014 were randomly selected from a pool of 132 patients. The exclusion criteria were pregnant females, patients who had not consented for the use of their data for research,

non-English-speaking patients whose cognitive test data could not be considered reliable, patients with preoperative cognitive impairment, and cases that were performed emergently.

Two measures for neurocognitive preservation were collected: the Cerebral Performance Category (CPC) scale and the modified Rankin Scale (mRS). Data collected with these instruments were used to classify patients into those who suffered significant neurocognitive loss and those who did not. A CPC of  $\leq 2$  and an mRS of  $\leq 3$  were neurocognitive preservation thresholds.

LivaNova S5<sup>®</sup> heart-lung machines (HLM) were used to calculate blood flow (blood flow rate [ $\text{Qb}$ ]) for all CPB procedures with an arterial 1/2" ID tubing roller pump (LivaNova, Arvada, CO). The Databahn Data Management System<sup>®</sup> (LivaNova) was linked to the S5 HLM to collect additional pertinent data. Terumo Capiiox<sup>®</sup> oxygenators (Terumo Cardiovascular Systems, Ann Arbor, MI) were used with X-Coating<sup>®</sup> (Terumo). Cardiectomy suction was returned to the venous reservoir which was connected to the oxygenator. Arterial and venous blood samples were measured by a Radiometer<sup>®</sup> ABL800 (Brea, CA) bench blood gas analyzer.

All procedures were limited to aortic surgery. Anesthesia was induced and maintained consistent with institutional and physician practice. Maintenance anesthesia while on normothermic ( $35\text{--}37^\circ\text{C}$ ) CPB included anesthetic gases (isoflurane, sevoflurane, or desflurane) with bolus administration of opioid and/or benzodiazepine analgesia, as needed. Laminar (non-pulsatile) CPB was established after a standard median sternotomy using dual atrial venous cannulation. Body temperature was measured using a nasopharyngeal and bladder temperature probe.

Target pump flows were between 2.0 and 3.0 L/min/ $\text{m}^2$  with a target mean arterial pressure, measured in either the right or left radial, or right or left femoral artery, of 50–70 mmHg. Initial oxygenator gas flows began at a 1:1 flow ratio to pump flow and then were adjusted to maintain an arterial oxygen tension greater than 150 mmHg and a corrected arterial carbon dioxide tension of between 35 and 45 mmHg.

Anticoagulation was accomplished using 400 international units of porcine heparin per kilogram of body weight as an initial dose, adequate to achieve a target activated clotting time of 480 seconds or greater. Subsequent heparin injections were given to maintain adequate anticoagulation for the duration of the case. At the end of CPB and before approximating the sternum, heparin was reversed with protamine sulfate in a ratio of 1:1 with the initial heparin dose.

Demographic and operative variables collected from the target population of CPB patients included age, height, weight, gender, and body surface area (BSA).  $\text{DO}_2$  and other derived parameters were recorded in the perfusion

**Table 1.** Summary of clinical characteristics for the study sample (n = 100).

|                                                                                          | Value         |
|------------------------------------------------------------------------------------------|---------------|
| Pre-operative period                                                                     |               |
| Age (years)                                                                              | 62.0 ± 11.7*  |
| Male/female                                                                              | 69.8%/30.2%†  |
| BSA (kg/m <sup>2</sup> )                                                                 | 2.1 ± .4*     |
| Hypertension                                                                             | 43%†          |
| Diabetes mellitus                                                                        | 11%†          |
| Previous stroke                                                                          | 9.4%†         |
| Previous seizure                                                                         | 4%†           |
| CPC                                                                                      | 1‡            |
| mRS                                                                                      | 0‡            |
| Operative period                                                                         |               |
| CPB time, minutes                                                                        | 227.7 ± 50.8* |
| Aortic cross-clamp time (minutes)                                                        | 179 ± 42.1*   |
| Duration of normothermic CPB, minutes (35–37°C)                                          | 35.7 ± 8.8*   |
| Duration of mild hypothermic CPB, minutes (32–34.9°C)                                    | 17.1 ± 6.6*   |
| Duration of moderate hypothermic CPB, minutes (28–31.9°C)                                | 19.2 ± 9.2*   |
| Duration of deep hypothermic CPB, minutes (19–27.9°C)                                    | 105.9 ± 31.0* |
| Duration of circulatory arrest (minutes)                                                 | 26.4 ± 18.6*  |
| DO <sub>2</sub> during normothermic CPB (mL O <sub>2</sub> /min/m <sup>2</sup> )         | 325.7 ± 63.4* |
| DO <sub>2</sub> during mild hypothermic CPB (mL O <sub>2</sub> /min/m <sup>2</sup> )     | 256.6 ± 35.8* |
| DO <sub>2</sub> during moderate hypothermic CPB (mL O <sub>2</sub> /min/m <sup>2</sup> ) | 265.4 ± 15.9* |
| DO <sub>2</sub> during deep hypothermic CPB (mL O <sub>2</sub> /min/m <sup>2</sup> )     | 228.5 ± 12.6* |
| Postoperative period                                                                     |               |
| Incidence of stroke                                                                      | 6%            |
| Negative survival to discharge                                                           | 4%            |
| Length of stay after surgery (days)                                                      | 8.9 ± 7.4*    |
| CPC 1                                                                                    | 83%†          |
| CPC ≥ 2                                                                                  | 13%†          |
| mRS 0–2                                                                                  | 83%†          |
| mRS ≥ 3                                                                                  | 13%†          |

\*Mean plus SD.

†Percentage of sample.

‡Mean.

record. Measures recorded at the time of blood sampling included arterial hemoglobin (Hgb) and hematocrit (Hct), blood flow rate, indexed flow rate, arterial oxygen tension, arterial oxygen saturation, arterial carbon dioxide tension, mixed venous oxygen tension, oxygen saturation, and carbon dioxide tension, as well as fraction of inspired oxygen (FiO<sub>2</sub>) and cerebral saturation values, when available. Other measures such as duration of aortic cross clamp and anesthetic gas delivery rate while on CPB were collected, as well.

A membrane oxygenator was used to provide temperature management of the blood, as well as oxygen and carbon dioxide gas exchange. All adjustments including increasing arterial carbon dioxide (partial pressure of arterial carbon dioxide [PaCO<sub>2</sub>]) levels that have dropped below a certain value (i.e., <35 mmHg), increasing blood flow rate, increasing mean arterial pressure, increasing FiO<sub>2</sub>, vasodilation, and transfusion to increase Hct levels were accomplished using the existing protocols.

All perfusion record data were calculated using non-proprietary formulas. The calculations for DO<sub>2i</sub> were based

**Table 2.** Chi-square test of association (100 patients).

| Scale               | DO <sub>2</sub> Met | DO <sub>2</sub> Not Met | Total |
|---------------------|---------------------|-------------------------|-------|
| CPC ≤ 2 and mRS ≤ 3 | 58 (54.78) [.19]    | 25 (28.22) [.37]        | 83    |
| CPC > 2 and mRS > 3 | 8 (11.22) [.92]     | 9 (5.78) [1.79]         | 17    |
| Total               | 66                  | 34                      | 100   |

on blood gas analysis being performed using a blood gas analyzer (alpha stat). Both arterial and venous oxygen contents were calculated according to the following oxygen content formula:  $(1.34 \times \text{Hgb} \times \text{SaO}_2) + (.003 \times \text{PaO}_2)$  or  $(1.34 \times \text{Hgb} \times \text{SVO}_2) + (.003 \times \text{PVO}_2)$ .

Because the primary goal of this research was to examine the relationship between DO<sub>2</sub> at or above versus below the critical DO<sub>2i</sub> level during CPB and neurocognitive preservation versus loss, chi-square tests of association were used to assess the relationship between these two categorical binaries variables. All data analysis was performed using SPSS software (IBM, Armonk, NY). Because neurocognitive preservation was evaluated with two instruments, two chi-square tests were used to examine the relationship between DO<sub>2</sub> and each one of the two measures of cognitive preservation.

## RESULTS

The clinical characteristics for the study sample are summarized in Table 1. Both DO<sub>2crit</sub> (met or not met) and neurocognitive outcomes (preservation or loss) were binary categorical. The two neurocognitive tests resulted in the same classification of patients in terms of neurocognitive preservation. Consequently, the analysis was ultimately reduced to a single chi-square test of association. In the initial data analysis, 10 patients who experienced either stroke or expired in the perioperative course were included.

Table 2 shows the neurocognitive outcomes for the entire data set (100 cases) and DO<sub>2</sub> group. In all, there were six patients who suffered strokes and four patients who died in the perioperative course. The level of statistical significance was alpha .05, with the test result failing to reach statistical significance,  $X^2(1, 100) = 3.27$ ,  $p = .07$ .

However, multifactorial mechanisms are potentially responsible for stroke and death in the perioperative course, other than ischemia secondary to low global CPB DO<sub>2i</sub>. As such and with a focus on providing a clearer and more concise evaluation, the decision was made to undergo a secondary data analysis after removing these cases from the initial 100. The values in Figure 1 represent the mean CPB DO<sub>2i</sub> for the remaining 90 patients: 83 (mean DO<sub>2i</sub> = 318.4 mL O<sub>2</sub>/min/m<sup>2</sup>) who demonstrated neurocognitive

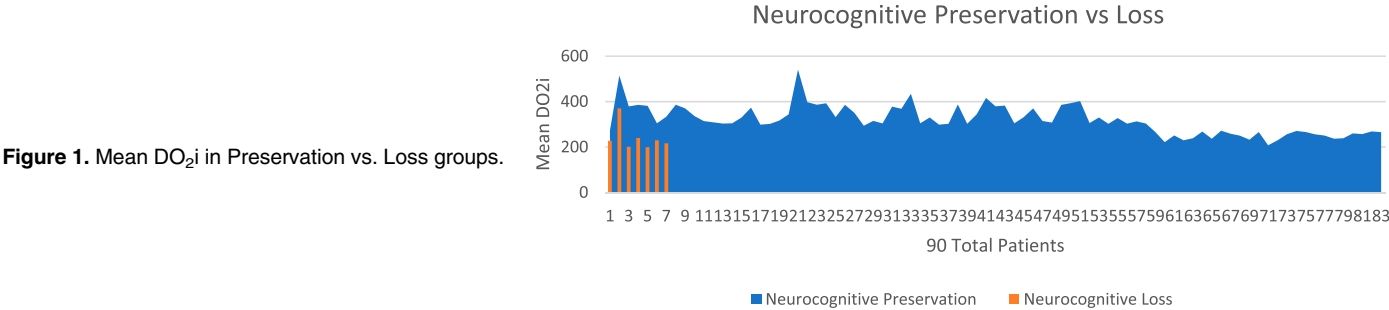


Figure 1. Mean DO<sub>2i</sub> in Preservation vs. Loss groups.

preservation and 7 (mean DO<sub>2i</sub> = 240.6 mL O<sub>2</sub>/min/m<sup>2</sup>) with neurocognitive loss.

The final chi-square analysis at alpha .05, reached statistical significance,  $\chi^2(1, 90) = 8.84, p = .003$  (Table 3). In addition, receiver operator characteristic curve (Figure 2) with the Youden index identified a global indexed DO<sub>2crit</sub> value of 239.9 mL O<sub>2</sub>/min/m<sup>2</sup> predicting neurocognitive preservation (area under receiver operator characteristic [AUROC] = .87, 95% cardiac index [CI] [.78–.93],  $p < .0004$ ) in this patient cohort.

DISCUSSION

The failure to reach statistical significance for the initial data set may be associated with at least two known phenomena, neither of which were controlled and are worth introducing. The first is the  $Q_{10}$  effect, and the second is cerebral autoregulation. The  $Q_{10}$  effect in human brain tissue can be defined as a coupling of the energy metabolism and blood flow under the influence of decreasing temperature and can be approximated by the following equation:  $J_{O_2} = J_{O_{20}} (Q_{10})^{-.1(T_o - T)}$ , where  $Q_{10}$  is the temperature coefficient,  $T$  and  $T_0$  are two distinct and different temperatures, and  $J_{O_2}$  and  $J_{O_{20}}$  are two distinct and different values of the cerebral metabolic rate of oxygen utilization (CMRO<sub>2</sub>) (21).

Between cerebral temperatures of 27°C and 37°C, the mean  $Q_{10}$  coefficient for CMRO<sub>2</sub> measurements is approximately 2.2 (22), meaning that at approximately 34°C, cerebral oxygen consumption is reduced by approximately 25%, and at approximately 29°C, there is approximately 50% reduction in cerebral oxygen consumption (21). As such and in relation to DO<sub>2crit</sub>, that would suggest that DO<sub>2crit</sub> is likely reduced by 50% at 29°C and can perhaps

be approximated at 136 mL O<sub>2</sub>/min/m<sup>2</sup>. All observations in this study met a DO<sub>2</sub> of at least this value. In addition, during CPB, the approximate mean amount of time spent below 34.9°C was approximately 75%. Because neurocognitive function generally will follow the course of neuronal survival (20), it may be reasonable to suggest that hypothermia may have played a role in neurocognitive preservation by decreasing the metabolic demand for oxygen.

Furthermore, Sungurtekin et al. (23) found that during CPB, cerebral blood flow was preserved near preoperative levels at a nasopharyngeal temperature of 27°C and both cerebral delivered oxygen (CDO<sub>2</sub>) and the CMRO<sub>2</sub> consumption were significantly reduced. However, measurements of jugular venous bulb saturations (SjvO<sub>2</sub>) were unchanged, leading the authors to suggest that cerebral autoregulation was intact at the studied parameters and

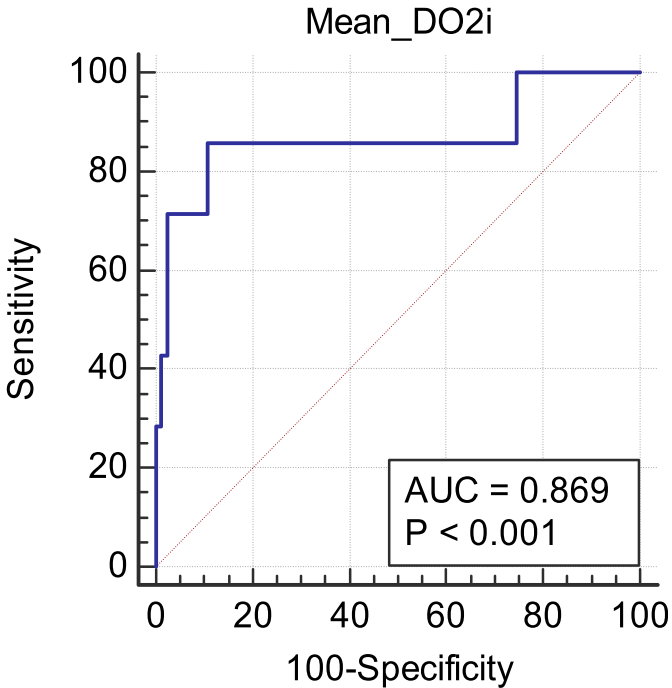


Figure 2. AUROC at DO<sub>2crit</sub> of 239.9 mL O<sub>2</sub>/min/m<sup>2</sup>.

Table 3. Chi-square test of association (90 patients).

| Scale               | DO <sub>2</sub> Met | DO <sub>2</sub> Not Met | Total |
|---------------------|---------------------|-------------------------|-------|
| CPC ≤ 2 and mRS ≤ 3 | 58 (54.41) [.24]    | 25 (28.59) [.45]        | 83    |
| CPC > 2 and mRS > 3 | 1 (4.59) [2.81]     | 6 (2.41) [5.34]         | 7     |
| Total               | 59                  | 31                      | 90    |

that the cerebral oxygen extraction rate was reduced commensurate with a reduction in CMRO<sub>2</sub>. In other words, the demand for oxygen was reduced proportionally with how quickly oxygen was being used in the cerebral tissue. These potential explanations appear consistent with the findings in this study.

Cerebral autoregulation may be defined as the ability to maintain a consistent supply of blood flow to the brain, despite the presence of certain physiologic changes (i.e., changes in blood pressure and temperature) (6). Increasingly, there is evidence to support the hypothesis that cerebral autoregulation may be both unique to each individual and intra-operatively dynamic (24). In addition, because cerebral autoregulation has been shown to be maintained down to a temperature of 27°C (23), and given that even at a higher temperature of 29°C CMRO<sub>2</sub> is likely to be 50% of normal values (21), there was quite likely both adequate blood flow and DO<sub>2</sub> to the cerebral tissues throughout the course of CPB which would be consistent with neurocognitive preservation, as well as non-statistically significant outcomes in the initial data set.

With respect to the analysis of the second data set, it is important to keep at least two things in mind. The first is that as demonstrated by Ono et al. (24), cerebral autoregulation may be best considered as individualized and the only way to know if the CDO<sub>2</sub>-to-CMRO<sub>2</sub> relationship is adequate to measure. Near-infrared spectroscopy values that have demonstrated efficacy in being used as a surrogate for SjvO<sub>2</sub> is one method that appears promising. Second, although gaining what is perhaps valuable information, retrospective studies are best suited to developing hypotheses which can then be tested in randomized, controlled, prospective studies.

To that end, the expected effect size used to estimate the minimum sample size for the present study was the medium value of .30. The sensitivity of the chi-square test at alpha .05 and power .80 was .28. In addition, because there was a trend toward significance, a very similar study would require a minimum of 1,300 cases for significance to be reached. Nonetheless, with the sensitivity and specificity of the Youden index criterion value of 239.9 mL O<sub>2</sub>/min/m<sup>2</sup> at 85.7 and 89.2, respectively, it seems reasonable to test the hypothesis that this value may demonstrate utility in alleviating an amply documented, yet unresolved, complication in this patient population.

The limitations of this study include, but are not limited to, the sensitivity of the instruments used to evaluate the neurocognitive status. The CPC and mRS tests lack robust temporal discrimination and were also not designed to distinguish between postoperative delirium and neurocognitive dysfunction. The reproducibility of the mRS has been previously questioned (25) as has the inter- and intra-reviewer agreement of the CPC (26). In addition, this study

was both retrospective and performed at a single center, either of which can potentially confound generalization.

The strengths of this study include, but are not limited to, the use of secondary data, from which no clinical adjustments or interventions were possible. In addition, only well-established, non-proprietary instruments and formulae were used. In conclusion, a larger sample size with controls may yield deeper insights into the hypothesis that a mean global CPB DO<sub>2</sub> of 239.9 mL O<sub>2</sub>/min/m<sup>2</sup> may play a role in predicting neurocognitive preservation in this patient population.

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