
Oxygenator-related gaseous microemboli and postoperative delirium after on-pump coronary artery bypass grafting: a prospective cohort study

Received: 21 January 2026

Accepted: 9 March 2026

Published online: 26 March 2026

Cite this article as: Tutuš V., Paunović M., Kulić S. *et al.* Oxygenator-related gaseous microemboli and postoperative delirium after on-pump coronary artery bypass grafting: a prospective cohort study. *BMC Anesthesiol* (2026). <https://doi.org/10.1186/s12871-026-03757-4>

Vladimir Tutuš, Milica Paunović, Slavko Kulić, Nina Rajovic, Nataša Milić, Vukašin Popović, Miloš Matković, Nemanja Aleksić, Radmila Karan, Jovana Stanisavljević, Svetozar Putnik, Danijela Trifunović Zamaklar & Dejan Marković

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

Oxygenator-related gaseous microemboli and postoperative delirium after on-pump coronary artery bypass grafting: A prospective cohort study

Vladimir Tutuš^{1,2} | Milica Paunović¹ | Slavko Kulić³ | Nina Rajović⁴ | Nataša Milić⁴ | Vukašin Popović¹ | Miloš Matković^{2,3} | Nemanja Aleksić^{2,3} | Radmila Karan^{1,2} | Jovana Stanisavljević^{2,5} | Svetozar Putnik^{2,3} | Danijela Trifunović Zamaklar^{2,6} | Dejan Marković^{1,2}

¹Department of Anesthesia, Clinic for Cardiac Surgery, University Clinical Centre of Serbia, Belgrade, Serbia

² Faculty of Medicine, University of Belgrade, Belgrade, Serbia

³Department of Surgery, Clinic for Cardiac Surgery, University Clinical Centre of Serbia, Belgrade, Serbia

⁴Institute for Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

⁵Department of Anesthesia, Emergency Center, University Clinical Centre of Serbia, Belgrade, Serbia

⁶Department of Cardiology, Clinic for Cardiac Surgery, University Clinical Centre of Serbia, Belgrade, Serbia

Correspondence: Milica Paunović, Clinic for Cardiac Surgery, University Clinical Centre of Serbia, Dr Koste Todorovića 8, 11000 Belgrade, Serbia. Email: paunovicmilica9@gmail.com

Abstract

Background

The increasing preference for off-pump coronary artery bypass grafting (CABG) reflects efforts to reduce complications associated with cardiopulmonary bypass (CPB). A lower incidence of postoperative delirium (POD) after off-pump procedures suggests that embolic load during CPB may contribute to postoperative neurocognitive impairment. Oxygenator design may influence the generation and transmission of gaseous microemboli (GME) during CPB. This study aimed to determine whether differences in oxygenator design affect the GME-handling characteristics of the CPB circuit and to evaluate the clinical implications of microembolic burden in patients undergoing on-pump CABG.

Methods

In this prospective, non-interventional observational study, 102 adult patients undergoing first-time isolated on-pump CABG were included. Patients were supported with one of three contemporary membrane oxygenators (Capiox FX25, Inspire 8, or Inspire 8F). Gaseous microemboli number and cumulative volume were continuously measured proximal and distal to the oxygenator using an ultrasonic microbubble counter. Postoperative delirium was assessed every 12 hours during the first postoperative week using the Confusion Assessment Method for the ICU and the Richmond Agitation–Sedation Scale by assessors blinded to oxygenator type.

Results

Baseline characteristics, operative variables, and venous GME burden were comparable among groups. Use of the Capiox FX25 oxygenator was associated with significantly lower arterial GME volume and the greatest reduction in microembolic volume compared with both Inspire oxygenators. Inspire 8 demonstrated the lowest reduction in GME number. Postoperative delirium occurred in 29.4% of patients and was least frequent in the Capiox FX25 group.

Conclusions

Oxygenator design significantly influences intraoperative gaseous microembolic burden and is associated with differences in postoperative delirium after on-pump CABG. Oxygenator selection

may represent a modifiable intraoperative factor affecting postoperative neurocognitive outcomes.

Trial registration

As this was a non-interventional, observational study with no deviation from standard clinical practice, registration in a public clinical trial registry was not required.

Keywords

Coronary artery bypass grafting (CABG); cardiopulmonary bypass (CPB); gaseous microemboli (GME); membrane oxygenator; postoperative delirium (POD)

ARTICLE IN PRESS

Background

Advances in cardiopulmonary bypass (CPB) technology have substantially improved the safety and outcomes of contemporary cardiac surgery. Modern CPB systems predominantly employ microporous hollow-fiber membrane oxygenators with extraluminal blood flow, designed to provide efficient gas exchange while minimizing blood trauma, pressure drop, and priming volume [1,2]. Despite these technological refinements, CPB-associated neurological complications, particularly postoperative delirium (POD), remain a major clinical concern.

The growing preference for off-pump coronary artery bypass grafting (CABG) reflects ongoing efforts to reduce CPB-related morbidity. Several studies have reported a lower incidence of POD following off-pump procedures [3], supporting the hypothesis that embolic phenomena during CPB play a central role in postoperative neurocognitive impairment [4]. Reported incidence rates of POD after cardiac surgery vary widely, ranging from 5% to 50%, largely due to heterogeneity in assessment methods and frequent underrecognition of hypoactive (i.e., “silent”) delirium [5,6]. Importantly, POD is not a benign transient complication; it is associated with prolonged mechanical ventilation, respiratory insufficiency, sternal instability, increased need for reintervention, longer intensive care unit (ICU) and hospital stays, long-term cognitive decline, reduced quality of life, and increased healthcare costs [7,8].

Gaseous microemboli (GME) are increasingly recognized as a key contributor to CPB-related cerebral injury. Beyond mechanical obstruction of cerebral microvasculature, GME may induce endothelial dysfunction, disrupt the blood–brain barrier, promote interstitial edema, and trigger inflammatory cascades involving leukocyte aggregation, complement activation, platelet activation, oxidative stress, and proteolytic enzyme release [9–11]. Collectively, these mechanisms provide a plausible biological link between intraoperative microembolic burden and postoperative neurological dysfunction.

Given this pathophysiological framework, the design and performance characteristics of membrane oxygenators may critically influence the embolic load delivered to the patients' cerebral circulation during CPB. Features such as membrane surface area, priming volume, surface coating, and the presence or absence of integrated arterial filtration may affect both the number and the size of microemboli transmitted to the patient. However, comparative clinical data evaluating the impact of different contemporary oxygenator designs on GME handling and neurological outcomes remain limited.

Therefore, the primary aim of this study was to evaluate whether differences in oxygenator design influence the generation and filtration of gaseous microemboli within the CPB circuit. The secondary aim was to assess the clinical relevance of oxygenator-specific microembolic burden by examining its association with postoperative delirium in patients undergoing on-pump CABG.

Methods

Study Design and Population

This prospective, observational, single-center study included consecutive adult patients undergoing isolated on-pump coronary artery bypass grafting (CABG) at a tertiary cardiac surgery center between January 1 and July 31, 2024.

Eligible patients were ≥ 18 years of age and scheduled for elective isolated CABG requiring cardiopulmonary bypass. Exclusion criteria were redo procedures, off-pump or minimally invasive CABG, emergent surgery, left ventricular ejection fraction $< 30\%$, documented history of neurological or psychiatric disorders and hemodynamically significant carotid artery stenosis (verified by routine preoperative carotid artery color Doppler ultrasound).

All patients were evaluated preoperatively by a cardiac surgeon to confirm the indication for CABG and by an anesthesiologist to assess suitability for general anesthesia. Demographic data, anthropometric measurements, comorbidities, and standard preoperative laboratory parameters were collected prospectively.

Oxygenator selection followed a predefined institutional perfusion protocol based on routine availability and logistical considerations and was not randomized. No deviations from standard clinical practice were introduced for the purposes of this study.

Anesthesia and Cardiopulmonary Bypass Management

Cardiopulmonary bypass was conducted using LivaNova Sorin Stockert S5 (LivaNova, London, United Kingdom) heart-lung perfusion machine with a roller pump, according to a standardized institutional protocol, including systemic heparinization to achieve an activated clotting time >480 s, aortic and right atrial cannulation, mild systemic hypothermia (32–34 °C), non-pulsatile pump flow of $2.4 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ indexed to body surface area, and mild hemodilution with a target hematocrit of 22–28%. Myocardial protection was achieved using intermittent antegrade St. Thomas II crystalloid cardioplegia administered every 20 minutes during aortic cross-clamping. Mean arterial perfusion pressure was maintained between 50 and 80 mmHg throughout CPB.

At the conclusion of CPB, anticoagulation was reversed with protamine sulfate. Intraoperative blood salvage was routinely used in all patients.

Oxygenators

The same conventional CPB circuit configuration was used for all patients, with the exception of the oxygenator. The employed oxygenators were one of three commercially available adult membrane oxygenators routinely used in contemporary CPB practice:

- Capiiox FX25 (Terumo Cardiovascular, Ann Arbor, MI, USA) – group CFX25
- Inspire 8 (LivaNova, London, United Kingdom) – group I8
- Inspire 8F (LivaNova, London, United Kingdom) – group I8F

Key technical specifications of the oxygenators are summarized in Table 1.

Table 1. Basic oxygenator specifications [12,13]

| | Oxygenator | | |
|--|---|---|--|
| | Capiox FX25 | Inspire 8 | Inspire 8F |
| <i>Membrane surface area (m²)</i> | 2.5 | 1.75 | 1.75 |
| <i>Maximum blood flow rate (l/min)</i> | 7 | 8 | 8 |
| <i>Static priming volume (ml)</i> | 260 | 219 | 351 |
| <i>Coating material</i> | Poly(2-methoxyethylacrylate) (PMEA) polymer | Phosphorylcholine (PC) polymer | Phosphorylcholine polymer |
| <i>Arterial filter</i> | Integrated <ul style="list-style-type: none"> • Pore size 32 μm • Surface area 600 cm^2 | Non-integrated <ul style="list-style-type: none"> • Pore size 27 μm • Surface area 655 cm^2 | Integrated <ul style="list-style-type: none"> • Pore size 38 μm • Surface area 97 cm^2 |

Intraoperative Variables

Recorded intraoperative variables included duration of surgery, CPB time, aortic cross-clamp time, reperfusion time, arterial partial pressure of oxygen during CPB, total cardioplegia volume, core temperature, intraoperative blood salvage volume and intraoperative packed red blood cells transfusion rates. Metabolic parameters, including arterial lactate and glucose concentrations, were measured during CPB.

Microembolic Load Measurements

Gaseous microemboli (GME) were quantified using an ultrasonic microbubble counter (GAMPT BC200, GAMPT mbH, Merseburg, Germany). Two ultrasonic probes were placed at standardized locations on the CPB circuit tubing proximal (venous line) and distal (arterial line) to the oxygenator.

Microbubble detection was performed continuously throughout CPB. The following primary parameters were recorded:

- total number of detected microbubbles,
- cumulative microbubble volume (μL).

Derived parameters included:

- number reduction (%): percentage decrease in microbubble count from venous to arterial line,
- volume reduction (%): percentage decrease in cumulative microbubble volume,
- quality factor (QF, %): proportion of microbubbles with diameters between 20 and 500 μm registered by both probes, with bubbles exceeding the measurable range assigned the maximum detectable diameter (from which the cumulative volume is calculated),
- mean diameter index (MDI, %): percentage reduction in mean microbubble diameter between venous and arterial measurements.

Postoperative Management and Outcomes

Postoperative care followed standardized institutional protocols. Patients were screened twice daily at 12-hour intervals during the first postoperative week by a trained physician for signs of delirium, including both hypoactive and hyperactive subtypes. Clinicians responsible for delirium assessment were not involved in intraoperative management and were blinded to the type of oxygenator used during surgery.

Postoperative delirium was diagnosed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), while delirium subtype and severity were evaluated using the Richmond Agitation–Sedation Scale (RASS) [14,15]. Analgesia consisted of paracetamol and tramadol according to institutional practice. Patients exhibiting hyperactive delirium were treated with dexmedetomidine infusion or additional pharmacological management following psychiatric consultation when required.

Recorded postoperative outcomes included duration of mechanical ventilation, total mediastinal and pleural drainage volume, length of intensive care unit stay (days), total hospital length of stay (days), and incidence of postoperative atrial fibrillation.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Clinical Centre of Serbia (IRB No. 307/26). Written informed consent was obtained from all participants prior to inclusion. As this was a non-interventional observational study with no deviation from standard clinical practice, registration in a public clinical trials registry was not required.

Statistical analysis

Continuous variables are presented as mean values with 95% confidence intervals, while categorical variables are expressed as counts and percentages. Normality of data distribution was assessed prior to analysis. Comparisons among oxygenator groups were performed using analysis of variance (ANOVA) with least significant difference (LSD) post-hoc testing for continuous variables and the chi-square test for categorical variables. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Chicago, IL, USA).

Results

A total of 102 consecutive patients undergoing isolated on-pump CABG were included in the study (CFX25: $n = 34$; I8: $n = 33$; I8F: $n = 35$). Baseline sociodemographic characteristics, anthropometric parameters and comorbidities were comparable among the three groups, with no statistically significant differences observed (Table 2). All patients in our study were considered low risk according to EuroSCORE II as a validated surgical risk prediction model incorporating cardiac and extracardiac risk factors ($<2.5\%$). Preoperative laboratory values, including inflammatory, metabolic, renal, and hepatic parameters, did not differ between groups (all $p > 0.05$).

Table 2. Sociodemographic characteristics and comorbidities of study population according to the type of oxygenator

| Variable | Oxygenator | | | p |
|--|------------------------|---------------------|----------------------|-------|
| | Capiiox FX25 (n=34) | Inspire 8 (n=33) | Inspire 8F (n=35) | |
| Gender, n (%) | | | | |
| Male | 29 (85.3) | 25 (75.8) | 27 (77.1) | 0.577 |
| Female | 5 (14.7) | 8 (24.2) | 8 (22.9) | |
| Age (years), mean (95%CI) | 62.68 (59.44-65.91) | 65.24 (61.15-69.33) | 63.71 (60.03-67.40) | 0.607 |
| BMI, mean (95%CI) | 28.24 (26.57-29.91) | 26.75 (25.28-28.22) | 28.42 (27.03-29.82) | 0.229 |
| BSA (m²), mean (95%CI) | 2.05 (1.95-2.15) | 1.94 (1.88-2.02) | 2.05 (1.97-2.14) | 0.155 |
| EuroSCORE II, mean (95%CI) | 1.55 (1.20-1.90) | 1.56 (1.31-1.81) | 1.23 (1.07-1.39) | 0.120 |
| Anemia, n (%) | 6 (17.6) | 7 (21.2) | 6 (17.1) | 0.902 |
| Diabetes mellitus, n (%) | 13 (38.2) | 14 (42.4) | 18 (51.4) | 0.525 |
| Atrial fibrillation, n (%) | 5 (14.7) | 3 (9.1) | 1 (2.9) | 0.209 |

Intraoperative and postoperative characteristics

Intraoperative and postoperative variables according to oxygenator type are summarized in Table 3. The duration of cardiopulmonary bypass, aortic cross-clamp time, reperfusion time, arterial oxygen tension during CPB, core temperature, operative duration, blood salvage volume, packed red blood cells transfusion rates and postoperative recovery parameters did not differ significantly among groups (all $p > 0.05$).

Significant difference was observed in cardioplegia volume administered during CPB ($p = 0.008$), with patients in the I8F group receiving a higher volume compared with both the CFX25 and I8 groups. Intraoperative lactate levels also differed significantly among groups ($p = 0.011$), with lower lactate concentrations observed in the CFX25 group compared with both Inspire oxygenator

groups. No significant differences were found in intraoperative glucose levels, postoperative mechanical ventilation duration, ICU or hospital length of stay, drainage volume, or incidence of postoperative atrial fibrillation.

Table 3. Intraoperative and postoperative characteristics of study population according to the type of oxygenator

| Variable | Oxygenator | | | p* |
|--|------------------------------------|----------------------------------|--|--------------|
| | Capiox FX25 ^a (n=34) | Inspire 8 ^b (n=33) | Inspire 8F ^c (n=35) | |
| ECC (minutes), mean (95%CI) | 70.41 (64.58-76.24) | 68.42 (62.15- 74.70) | 74.46 (66.88-82.04) | 0.412 |
| AoCl (minutes), mean (95%CI) | 38.82 (34.86-42.79) | 37.82 (33.56- 42.08) | 40.69 (36.10-45.27) | 0.621 |
| pO ₂ (kPa), mean (95%CI) | 27.17 (25.28-29.05) | 28.04 (25.97- 30.11) | 27.37 (25.83-28.90) | 0.778 |
| Cardioplegia (ml), mean (95%CI) | 1075 (1003.2- 1146.8) | 1122.7 (1053.9- 1191.5) | 1247.1 (1150.6- 1343.7) ^{ab} | 0.008 |
| Reperfusion (minutes), mean (95%CI) | 28.21 (25.51-30.90) | 27.24 (24.39- 30.09) | 29.37 (25.62-33.12) | 0.624 |
| Temperature (°C), mean (95%CI) | 33.9 (33.6-34.3) | 33.9 (33.6-34.3) | 34.2 (33.7-34.6) | 0.598 |
| Cell Saver (ml), mean (95%CI) | 410.8 (347.8-473.9) | 457.1 (405.8- 508.4) | 430.4 (374.7-486.1) | 0.510 |
| Lactate ECC (mmol/l), mean (95%CI) | 1.90 (1.71-2.09) ^{bc} | 2.49 (2.16-2.81) | 2.36 (2.03-2.67) | 0.011 |
| Glycemia ECC (mmol/l), mean (95%CI) | 8.65 (5.64-11.66) | 6.84 (6.05-7.64) | 7.12 (6.49-7.74) | 0.317 |
| Duration of operation (minutes), mean (95%CI) | 261.91 (246.86- 276.96) | 252.73 (240.66- 264.79) | 260.57 (250.9- 270.24) | 0.524 |

| | | | | |
|--|---------------------|---------------------|---------------------|-------|
| Duration mechanical ventilation (hours), mean (95%CI) | 11.24 (9.60-11.88) | 11.33 (9.76-12.91) | 11.03 (9.26-12.80) | 0.964 |
| Time in intensive care unit (days), mean (95%CI) | 3.21 (2.58-3.84) | 3.41 (2.98-3.85) | 3.61 (2.96-4.25) | 0.607 |
| Time spent in hospital (days), mean (95%CI) | 6.88 (6.30-7.47) | 7.56 (6.72-8.40) | 7.44 (6.75-8.13) | 0.335 |
| Total mediastinal and pleural drainage (ml), mean (95%CI) | 696.8 (591.2-802.3) | 666.1 (565.3-767.0) | 671.8 (571.5-772.0) | 0.904 |
| Atrial fibrillation in hospital, n (%) | 10 (32.2) | 13 (43.3) | 10 (40.0) | 0.660 |
| Intraoperative doses of packed red blood cells, n (%) | 6 (17.65) | 7 (21.21) | 8 (22.85) | 0.862 |

*between group value

^{a,b,c} – within group differences

Gaseous microemboli measurements

Venous line GME number and volume did not differ significantly among the three oxygenator groups, providing a consistent baseline for evaluation of oxygenator-related microembolic filtration (Table 4).

In contrast, significant differences were observed in arterial GME burden. Arterial microbubble number differed among groups ($p = 0.036$), with higher counts detected in the I8 group compared with the CFX25 group. Arterial GME volume also differed significantly ($p < 0.001$) - patients supported with the CFX25 oxygenator exhibited the lowest arterial microbubble volume, significantly lower than both the I8 and I8F groups.

Oxygenator-dependent differences were further reflected in venoarterial GME reduction efficiency. Reduction in microbubble number differed significantly among groups ($p = 0.004$), with the I8 oxygenator demonstrating lower reduction efficiency compared with CFX25 and I8F

(Figure 1). Similarly, reduction in microbubble volume differed significantly ($p = 0.001$), with the highest volume reduction observed in the CFX25 group (Figure 2).

Quality factor (QF) and mean diameter index (MDI) did not differ significantly among groups, indicating comparable proportions of measurable microbubble sizes and similar effects on mean microbubble diameter.

Table 4. GME measurements and POD according to the type of oxygenator

| Variable, mean (95%CI) | Oxygenator | | | p* |
|---------------------------------|------------------------------------|-------------------------------------|-----------------------------------|------------------|
| | Capiox FX25 ^a (n=34) | Inspire 8 ^b (n=33) | Inspire F8 ^c (n=35) | |
| Venous number | 37988.3 (30603.1-45373.6) | 30950.1 (26271.7-35628.6) | 35889.4 (31044.9-40734.0) | 0.209 |
| Arterial number | 2652.1 (2159.3-3144.8) | 4189.8 (2877.5-5502.1) ^a | 2950.1 (2270.0-3630.1) | 0.036 |
| Venous volume (µl) | 15.61 (11.17-20.04) | 17.37 (11.08-23.67) | 14.60 (9.26-19.95) | 0.758 |
| Arterial volume (µl) | 0.25 (0.12-0.38) ^{b,c} | 1.21 (0.78-1.63) | 0.80 (0.53-1.08) | <0.001 |
| GME number reduction (%) | 92.78 (91.58-93.98) | 85.14 (79.75-90.53) ^{a,c} | 90.91 (88.76-93.06) | 0.004 |
| GME volume reduction (%) | 97.52 (95.86-99.18) ^{b,c} | 91.21 (88.19-94.23) | 93.12 (90.98-95.25) | 0.001 |
| QF (%) | 99.7 (99.44-99.97) | 99.32 (98.82-99.92) | 99.68 (99.52-99.84) | 0.189 |
| MDI (%) | 37.07 (33.72-40.42) | 23.26 (20.0-26.52) | 26.63 (22.24-31.03) | 0.398 |
| POD, n (%) | 4 (11.8) ^{b,c} | 14 (42.4) | 12 (34.3) | 0.017 |

*between group value

^{a,b,c} – within group differences

Postoperative delirium

Postoperative delirium occurred in 30 of 102 patients (29.4%). Of these, 11 patients (36.7%) exhibited hyperactive delirium, while 19 patients (63.3%) developed the hypoactive subtype.

The incidence of postoperative delirium differed significantly according to oxygenator type ($p = 0.017$). Patients in the CFX25 group experienced postoperative delirium less frequently compared with those in the I8 and I8F groups (Table 4). This finding paralleled oxygenator-specific differences in arterial GME volume and volume reduction efficiency.

ARTICLE IN PRESS

Discussion

This study demonstrates that differences in oxygenator design and performance characteristics are associated with clinically relevant differences in GME load during CPB. Among the evaluated devices, the Inspire 8 oxygenator was associated with the highest arterial GME number, reaching statistical significance compared with the Capiox FX25, while a consistent trend toward higher microembolic burden was also observed when compared with the Inspire 8F. In contrast, arterial GME volume was lowest in patients supported with the Capiox FX25, a finding that was statistically significant compared with both Inspire oxygenators. These findings suggest that oxygenator design influences not only the number of microbubbles, but also their cumulative volume, an increasingly recognized determinant of microvascular injury.

Differences in microembolic burden were further reflected in oxygenator-specific filtration efficiency. The Inspire 8 demonstrated the lowest reduction in GME number, whereas the Capiox FX25 achieved the highest reduction in GME volume. Although MDI did not differ significantly among groups, the direction of change favored the Capiox FX25, indicating a trend toward more effective reduction of mean microbubble size. Collectively, these findings support the concept that oxygenator-related microbubble modulation extends beyond simple bubble count and may involve size-dependent effects relevant to downstream cerebral microcirculation.

The clinical relevance of these observations is reinforced by our previously published multivariate analysis performed in the same study cohort, which identified arterial GME volume greater than 1 μL and venoarterial GME volume reduction below 95% as independent predictors of postoperative delirium [16]. When interpreted in this context, the present results acquire additional significance. Arterial GME volume exceeded the previously identified risk threshold in the Inspire 8 group, while both Inspire oxygenators demonstrated volume reduction below 95%. These oxygenator-specific characteristics parallel the observed differences in postoperative delirium incidence, suggesting a mechanistic link between intraoperative microembolic exposure and postoperative neurological vulnerability.

Gaseous microemboli were quantified using the Gampt BC200 ultrasonic microbubble counter, which is widely used for comparative assessment of CPB circuit components. While absolute quantification of microbubble volume remains methodologically challenging, this device is considered reliable for relative comparisons between circuit configurations [17,18]. The absence of significant differences in quality factor (QF) among groups indicates that the proportion of bubbles outside the measurable range was minimal and comparable, supporting the validity of intergroup comparisons.

The lack of differences in venous microbubble number and volume across groups provides a robust baseline, allowing attribution of arterial differences primarily to oxygenator-related handling of GME. The Inspire 8F oxygenator demonstrated improved GME reduction compared with the Inspire 8, despite sharing identical membrane surface area and coating material. The only relevant design difference between these devices is the integration of an arterial filter in the Inspire 8F, suggesting that integrated filtration contributes to improved microembolic handling. However, previous studies evaluating the clinical impact of integrated arterial filters have yielded inconsistent results, indicating that filtration efficiency likely depends on the interaction between multiple design parameters [19-21].

Both the Capiox FX25 and Inspire 8F incorporate integrated arterial filtration, yet the Capiox FX25 exhibited superior reduction of arterial GME volume. This difference may be explained by its larger membrane surface area and smaller pore size, which could enhance microbubble retention and fragmentation [22]. Although surface coating materials, phosphorylcholine polymer in the Inspire oxygenators and poly(2-methoxyethylacrylate) in the Capiox FX25, are primarily intended to improve biocompatibility and reduce platelet activation, their role in GME filtration remains unclear. Additionally, the lower priming volume, as seen with Inspire 8, has previously been associated with poorer GME removal, potentially contributing to the observed differences [23].

It should be acknowledged that intraoperative sources of GME extend beyond oxygenator performance. Surgical manipulation and perfusionist interventions represent major contributors to GME generation during CPB [10,24]. Because such interventions may introduce microbubbles distal to the venous measurement site, arterial GME burden likely reflects a combined effect of oxygenator characteristics and intraoperative perfusion practices. Nevertheless, standardized CPB management and comparable venous microbubble loads across groups support a dominant role of oxygenator design in determining arterial GME transmission in this study.

Microembolic activity during CPB has long been implicated in postoperative neurocognitive dysfunction [25]. Our findings further support the concept that cumulative microbubble volume, rather than absolute number, represents a more relevant determinant of neurological injury. In this study, volume-related microembolic parameters were most favorable in the Capiiox FX25 group, which also exhibited the lowest incidence of POD. Importantly, the majority of delirium cases were of the hypoactive subtype, which is subtle and easily overlooked [26,27], hence frequently underdiagnosed in routine clinical practice and may partially explain inconsistent associations reported in previous studies [28,29].

Other intraoperative factors may have contributed to postoperative outcomes. A well-established marker of tissue hypoperfusion, intraoperative lactate level was significantly lower in patients supported with the Capiiox FX25, suggesting favorable perfusion during CPB [30,31]. Conversely, a higher volume of cardioplegic solution was administered in the Inspire 8F group, a factor that may increase the risk of air entrainment [32]. These observations underscore that, while oxygenator design plays a central role in GME handling, microembolic burden is influenced by multiple interacting intraoperative variables.

From a clinical perspective, these findings suggest that oxygenator selection during on-pump CABG should not be viewed as a purely technical decision. Instead, oxygenator design may represent a modifiable factor influencing cerebral microembolic exposure and postoperative neurocognitive outcomes. Consideration of GME filtration efficiency, alongside conventional performance characteristics, may contribute to improved patient safety. In parallel, meticulous perfusion techniques remain essential to minimize intraoperative air entrainment.

Study limitations

Several limitations should be considered. This was a single-center observational study with a relatively modest sample size, which may limit generalizability and the detection of smaller intergroup differences. Although delirium assessment was standardized and performed twice daily using validated instruments, hypoactive delirium may still have been underrecognized. Detailed intraoperative hemodynamic and respiratory variables were not incorporated into the analysis, and oxygenator allocation was not randomized. Finally, while strong associations between GME parameters and postoperative delirium were observed, causality cannot be inferred from the study design.

Conclusion

In conclusion, this study demonstrates that oxygenator design features, including membrane surface area, priming volume, surface coating, and arterial filter configuration, are associated with measurable differences in gaseous microembolic burden during cardiopulmonary bypass. Given the observed association between increased GME exposure and postoperative delirium, oxygenator selection may represent a clinically relevant and modifiable determinant of neurocognitive outcome following on-pump CABG. Further multicenter studies are warranted to confirm these findings and refine oxygenator selection strategies aimed at reducing neurological morbidity.

List of abbreviations

AF - atrial fibrillation; ACT - activated clotting time; AST - aspartate aminotransferase; BIS - Bispectral Index; BMI - body mass index; BSA - body surface area; CABG - coronary artery bypass grafting; CAM-ICU - Confusion Assessment Method for the Intensive Care Unit; CFX25 - Capiiox FX25; CPB - cardiopulmonary bypass; CRP - C-reactive protein; ECC - extracorporeal

circulation; GME - gaseous microemboli; GFR - glomerular filtration rate; I8 - Inspire 8; I8F - Inspire 8F; ICU - intensive care unit; IRB - Institutional Review Board; LDH - lactate dehydrogenase; MDI - Mean Diameter Index; PMEA - Poly(2-methoxyethylacrylate) polymer; PC - phosphorylcholine polymer; POD - postoperative delirium; QF - Quality Factor; RASS - Richmond Agitation-Sedation Scale; TCI - target-controlled infusion.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants signed a written informed consent form. The study protocol was approved by the referent Institutional Review Board (IRB No. 307/26). Written informed consent was obtained from all participants prior to inclusion in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during this research are not publicly available due to institutional policies but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no financial support from funding agencies in the public, commercial, or not-for-profit sectors for the research, authorship, and/or publication of this article.

Authors' contributions

VT - conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing; MP – conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing; SK - conceptualization, data curation, investigation, project administration, resources, software, writing; NR - data curation, formal analysis, investigation, methodology, software, writing; NM - data curation, formal analysis, investigation, methodology, software, supervision, validation; VP – data curation, investigation, project administration, visualization, writing; MM - conceptualization, data curation, investigation, methodology, project administration, supervision, validation, writing; NA – conceptualization, methodology, project administration, supervision, validation, writing; RK – conceptualization, formal analysis, project administration, resources, software, writing; JS – investigation, software, validation, writing; SP – conceptualization, methodology, project administration, resources, software, supervision, validation, visualization; DZ – conceptualization, formal analysis, methodology, project administration, supervision, validation; DM – conceptualization, methodology, project administration, supervision, validation, writing

Acknowledgements

We would like to express gratitude to all employees of our hospital involved in the care of our patients.

References

1. Iwahashi H, Yuri K, Nosé Y. Development of the oxygenator: past, present, and future. *J Artif Organs*. 2004;7(3):111-20. doi: 10.1007/s10047-004-0268-6.
2. Gaylor JD, Hickey S, Bell G, Pei JM. Membrane oxygenators: influence of design on performance. *Perfusion*. 1994 May;9(3):173-80. doi: 10.1177/026765919400900304.
3. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, Schmitt DV, Mohr FW. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg*. 2004 Jan;127(1):57-64. doi: 10.1016/s0022-5223(03)01281-9.

4. Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL, McCollum CN. Cerebral injury during cardiopulmonary bypass: emboli impair memory. *J Thorac Cardiovasc Surg.* 2001 Jun;121(6):1150-60. doi: 10.1067/mtc.2001.114099.
5. Chen H, Mo L, Hu H, Ou Y, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. *J Cardiothorac Surg.* 2021 Apr 26;16(1):113. doi: 10.1186/s13019-021-01496-w.
6. McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, Pandharipande PP. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med.* 2013 Feb;41(2):405-13. doi: 10.1097/CCM.0b013e31826ab49b.
7. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth.* 2020 Oct;125(4):492-504. doi: 10.1016/j.bja.2020.06.063.
8. Brown CH 4th, Laflam A, Max L, Lyman D, Neufeld KJ, Tian J, Shah AS, Whitman GJ, Hogue CW. The Impact of Delirium After Cardiac Surgical Procedures on Postoperative Resource Use. *Ann Thorac Surg.* 2016 May;101(5):1663-9. doi: 10.1016/j.athoracsur.2015.12.074.
9. Mitchell SJ, Merry AF. Perspective on Cerebral Microemboli in Cardiac Surgery: Significant Problem or Much Ado About Nothing? *J Extra Corpor Technol.* 2015 Mar;47(1):10-5.
10. Lou S, Ji B, Liu J, Yu K, Long C. Generation, detection and prevention of gaseous microemboli during cardiopulmonary bypass procedure. *Int J Artif Organs.* 2011 Nov;34(11):1039-51. doi: 10.5301/ijao.5000010.
11. Barak M, Katz Y. Microbubbles: pathophysiology and clinical implications. *Chest.* 2005 Oct;128(4):2918-32. doi: 10.1378/chest.128.4.2918.
12. "Inspire Oxygenator for Cardiopulmonary Bypass | LivaNova US." *Www.livanova.com*, <https://www.livanova.com/cardiopulmonary/en-us/oxygenators/inspire> (accessed 29 November 2025).
13. *CAPIOX® FX Oxygenator.* (n.d.). Terumo Europe, Middle East & Africa. <https://www.terumo-europe.com/en-emea/products/capiox®-fx-oxygenator> (accessed 29 November 2025).

14. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med.* 2001 Jul;29(7):1370-9. doi: 10.1097/00003246-200107000-00012.
15. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* 2003 Jun 11;289(22):2983-91. doi: 10.1001/jama.289.22.2983.
16. Tutuš V, Paunović M, Rajović N, Milić N, Matković M, Karan R, Putnik S, Aleksić N, Trifunović Zamaklar D, Jugović M, Bilbija I, Nešić S, Marković D. Gaseous Microemboli and Postoperative Delirium in Coronary Artery Bypass Grafting. *J Clin Med.* 2025 Jul 18;14(14):5123. doi: 10.3390/jcm14145123.
17. Nishi RY. Ultrasonic detection of bubbles with doppler flow transducers. *Ultrasonics.* 1972 Jul;10(4):173-9. doi: 10.1016/0041-624x(72)90359-9.
18. Segers T, Stehouwer MC, de Somer FMJJ, de Mol BA, Versluis M. Optical verification and in-vitro characterization of two commercially available acoustic bubble counters for cardiopulmonary bypass systems. *Perfusion.* 2018 Jan;33(1):16-24. doi: 10.1177/0267659117722595.
19. Jabur GN, Sidhu K, Willcox TW, Mitchell SJ. Clinical evaluation of emboli removal by integrated versus non-integrated arterial filters in new generation oxygenators. *Perfusion.* 2016 Jul;31(5):409-17. doi: 10.1177/0267659115621614.
20. Stehouwer MC, Legg KR, de Vroeghe R, Kelder JC, Hofman E, de Mol BA, Bruins P. Clinical evaluation of the air-handling properties of contemporary oxygenators with integrated arterial filter. *Perfusion.* 2017 Mar;32(2):118-125. doi: 10.1177/0267659116664402.
21. Horton SB, Donath S, Thuys CA, Bennett MJ, Augustin SL, Horton AM, Schultz BJ, Bottrell SJ, Konstantinov I, d'Udekem Y, Brizard C. Integrated Oxygenator FX05. *ASAIO J.* 2011 Nov-Dec;57(6):522-6. doi: 10.1097/MAT.0b013e318232c1db.
22. Riley JB. Arterial line filters ranked for gaseous micro-emboli separation performance: an in vitro study. *J Extra Corpor Technol.* 2008 Mar;40(1):21-6.

23. Norman MJ, Sistino JJ, Acsell JR. The effectiveness of low-prime cardiopulmonary bypass circuits at removing gaseous emboli. *J Extra Corpor Technol.* 2004 Dec;36(4):336-42.
24. Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *Ann Thorac Surg.* 1999 Jul;68(1):89-93. doi: 10.1016/s0003-4975(99)00475-0.
25. Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke.* 1994 Jul;25(7):1393-9. doi: 10.1161/01.str.25.7.1393.
26. Kruis RW, Vlasveld FA, Van Dijk D. The (un)importance of cerebral microemboli. *Semin Cardiothorac Vasc Anesth.* 2010 Jun;14(2):111-8. doi: 10.1177/1089253210370903.
27. Van Dijk D, Kalkman CJ. Why are cerebral microemboli not associated with cognitive decline? *Anesth Analg.* 2009 Oct;109(4):1006-8. doi: 10.1213/ANE.0b013e3181b5af06.
28. Stransky M, Schmidt C, Ganslmeier P, Grossmann E, Haneya A, Moritz S, Raffer M, Schmid C, Graf BM, Trabold B. Hypoactive delirium after cardiac surgery as an independent risk factor for prolonged mechanical ventilation. *J Cardiothorac Vasc Anesth.* 2011 Dec;25(6):968-74. doi: 10.1053/j.jvca.2011.05.004.
29. Sanson G, Khlopenyuk Y, Milocco S, Sartori M, Dreas L, Fabiani A. Delirium after cardiac surgery. Incidence, phenotypes, predisposing and precipitating risk factors, and effects. *Heart Lung.* 2018 Jul-Aug;47(4):408-417. doi: 10.1016/j.hrtlng.2018.04.005.
30. Noguchi S, Saito J, Hashiba E, Kushikata T, Hirota K. Lactate level during cardiopulmonary bypass as a predictor of postoperative outcomes in adult patients undergoing cardiac surgery. *JA Clin Rep.* 2016;2(1):39. doi: 10.1186/s40981-016-0064-3.
31. Demers P, Elkouri S, Martineau R, Couturier A, Cartier R. Outcome with high blood lactate levels during cardiopulmonary bypass in adult cardiac operation. *Ann Thorac Surg.* 2000 Dec;70(6):2082-6. doi: 10.1016/s0003-4975(00)02160-3.
32. Mukdad L, Toppen W, Sanaiha Y, Mantha A, Bland S, Shemin R, Benharash P. Incidence of Cerebral Microemboli in Single-Dose vs. Multidose Cardioplegia in Adult Cardiac Surgery. *J Extra Corpor Technol.* 2018 Sep;50(3):143-148.