

# Can the Oxygenator Screen Filter Reduce Gaseous Microemboli?

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**Abstract:** Gaseous microemboli (GME) define small bubbles as  $<200\ \mu\text{m}$  in size. GME are reported to increase morbidity after cardiopulmonary bypass (CPB) and cardiac surgery. To prevent intrusion of GME into the systemic circulation during CPB, arterial line filtration is generally recommended. New trends in oxygenator design promote location of arterial filtration as an integral part of the oxygenator housing. The present experimental study aimed to evaluate the GME removal properties of an integrated arterial screen filter in a standard microporous oxygenator. The GME properties of Terumo Capiox<sup>®</sup> FX25 with an integrated arterial screen filter was assessed in an experimental setup and compared with Capiox<sup>®</sup> RX25, in which no arterial screen filter is present. A blood analog prime solution was recirculated using a roller pump at 4 and 6 L per minute flow rate, respectively, through a customized CPB circuit comprising oxygenator, reservoir, and connecting tubing. A controlled volume of air was introduced into the circuit. The GME activity

was measured and computed using a Gampt BCC200<sup>®</sup> ultrasonic device placing one probe at the venous inlet and one other at the arterial outlet of the oxygenator. Transmembrane delta values of GME activity were used to calculate the removal efficacy based on counts and volume of GME. Use of screen filtration reduced the GME volume by  $99.1\% \pm .1\%$  compared with  $98.0\% \pm .1\%$  for controls at 4 L/min flow rate ( $p < .001$ ). At 6 L/min, the reduction was  $97.9\% \pm .1\%$  compared with  $97.0\% \pm .1\%$  ( $p < .001$ ). In contrast, the reduction of GME counts was less effective after screen filtration compared with controls:  $89.6 \pm .6\%$  versus  $91.4 \pm .4\%$  at 4 L/min and  $55.6\% \pm 1.6\%$  versus  $76.0\% \pm 1.4\%$  at 6 L/min, respectively ( $p < .001$ ). The tested oxygenator with incorporated arterial screen filter reduced GME activity based on the calculated volume at the same time as counts of GME increased. **Keywords:** arterial filtration, cardiopulmonary bypass, gaseous microemboli, gaseous microemboli detection. *JECT. 2014;46:60–66*

The incidence of adverse cerebral events after cardiac surgery ranges between 1% and 3% (1). The occurrence of cognitive disturbances is much more common. The reported rate is wide and varies between 20% and 60% (2,3). One potential mechanism for the development of cognitive deficits after cardiac surgery is gaseous microemboli (GME) arising from the use of cardiopulmonary bypass (CPB) (4,5).

Arterial line filtration is the recommended preventive action to reduce the number of GME entering the systemic circulation (6,7). Conventional arterial line filters are as a rule standalone components integrated as part of the extracorporeal circuit. A new oxygenator design enables arterial filters to be fit within the oxygenator housing.

The Terumo Capiox<sup>®</sup> FX oxygenator (Terumo Medical Corporation, Ann Arbor, MI) incorporates a  $32\text{-}\mu\text{m}$  screen filter wrapped around the hollow fiber bundle. The screen filter area is  $600\ \text{cm}^2$ . The oxygenator is identical to the

Capiox<sup>®</sup> RX series apart from the in situ screen filter. Air trapped inside the filter is pushed through the microporous hollow fiber enforced by interwall pressure differences and eventually vented through the oxygenator's gas outlet.

The present experimental investigation aimed to examine the GME removal efficacy comparing the Terumo Capiox<sup>®</sup> FX with Terumo Capiox<sup>®</sup> RX as representatives of two oxygenators with or without integrated arterial screen filter.

## MATERIAL AND METHODS

### The Bench Model

The Terumo Capiox<sup>®</sup> RX 25 and Capiox<sup>®</sup> FX 25 oxygenators, with integrated venous and cardiotomy reservoir, were tested using the Stöckert<sup>®</sup> S5 roller pump (Sorin Group, München, Germany) and Jostra<sup>®</sup> HCU30 heater cooler unit (Jostra Maquet Getinge Group, Rastatt, München, Germany). A two-channel microbubble ultrasonic pulsed Doppler device, Gampt BC200<sup>®</sup> (Gampt mbH, Merseburg, Germany), was used for GME analysis. The Stöckert Data Management System<sup>®</sup> (DMS) (Sorin Group) was interfaced to the heart–lung machine for

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recording of intracircuit temperature, preoxygenator membrane pressure, and pump and gas flow rate. The DMS was set to record once every minute.

The CPB circuit was flushed with carbon dioxide. Ringer's acetate (1200 mL) was added and recirculated through a 0.2- $\mu$ m prebypass filter (Pall Corporation<sup>®</sup>, Portsmouth, U.K.) for 5 minutes. The prebypass filter was excluded followed by addition of glycerol (VWR<sup>®</sup> International AB, Stockholm, Sweden) (500 mL). The resultant priming solution comprised 30% of glycerol equivalent to a viscosity of 2.934 mPa·s at 20°C (8). After another 20 minutes of recirculation and having adjusted the volume in the venous reservoir to 300 mL, the experiment began.

Preoxygenator pressure was adjusted to 300 mmHg at the targeted pump flow rate by stepwise occlusion of the venous line (9). The HCU water temperature was set to 38°C to reach the target temperature at 37°C, the sweep gas flow to 1.0 L per minute, and FiO<sub>2</sub> to 0.21.

### Randomization

Two groups were formed: Terumo FX 25 oxygenator (n = 1; study group) and Terumo RX 25 oxygenator (n = 1; control group). The experiment was performed at two different pump flow rates: 4 and 6 L per minute, repeated 10 times. The sequence of pump flow rates levels was

chosen randomly. Study and control groups (n = 1 + 1) used one complete new sterile CPB circuit each.

### Intervention

Air was introduced into the circuit through a 0.6 × 25-mm needle, Microlance<sup>®</sup> 3 (BD, Franklin Lakes, NJ) mounted in a 3/8 × 3/8 × 1/4-inch Y-connector Cobe Lab<sup>®</sup> (Sorin Group, Milano, Italy) positioned midstream at the reservoir inlet. The needle was sealed with a Luer-Lok cap (Figure 1). Control of air inlet was accomplished by opening and closing the Luer-Lok cap. This method of introducing air is previously described (10).

### Gaseous Microemboli Analysis

Ultrasonic sensors were positioned 5 cm proximally of the venous inlet (preoxygenator) and 10 cm distally of the arterial outlet (postoxygenator). The 10- to 250- $\mu$ m range of GME detection level was selected. The Gampt BCC200<sup>®</sup> was connected to a power supply, Safeline TT500<sup>®</sup> (Power Support Scandinavia, Stockholm, Sweden) to avoid interference from grid spikes in the operating room. Each measurement started with 1 minute of steady-state registration at 3 L per minute pump flow rate. Steady state was defined as  $\leq 5$  GME/second preoxygenator and  $\leq 1$  GME/second postoxygenator. The timeframe for each registration was

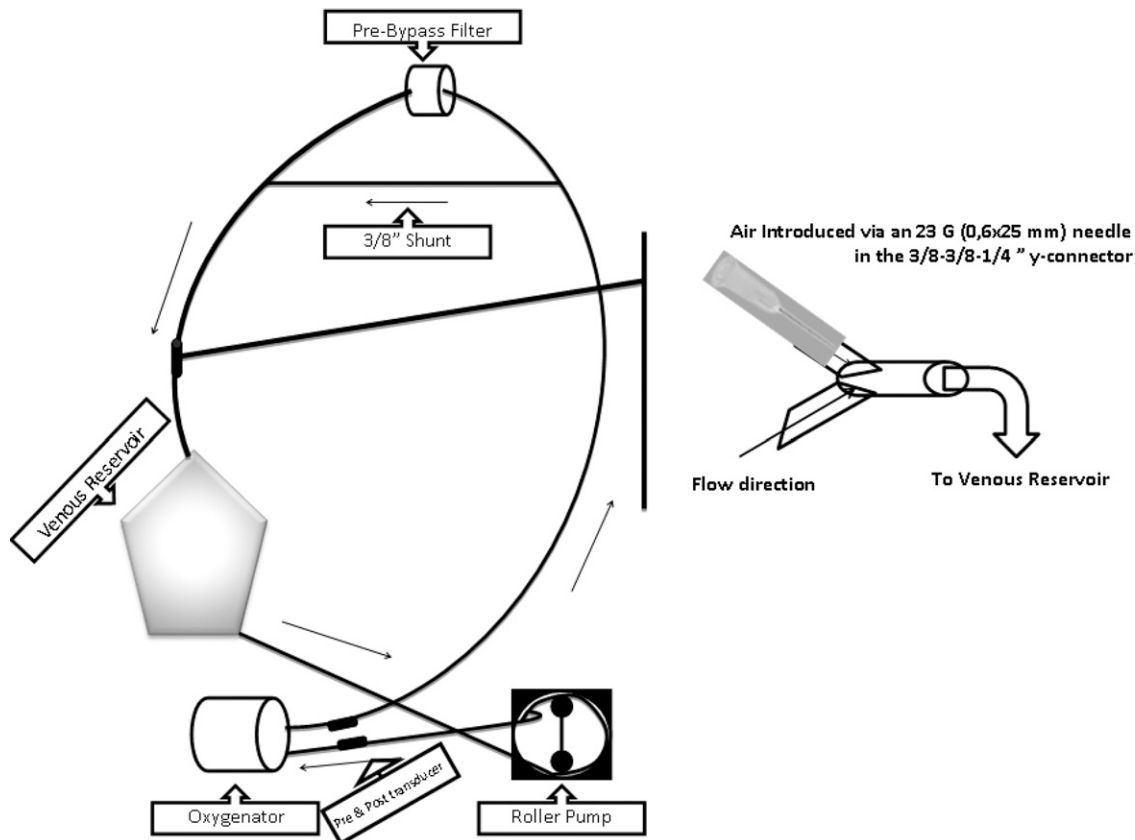


Figure 1. Schematic drawing of the experimental model setup.

4 minutes. Data were recorded and processed using the BCView<sup>®</sup> 3.4.2 (Gampt mbH, Merseburg, Germany) software and thereafter exported to Microsoft<sup>®</sup> Office Excel 2003 (Microsoft, Redmond, WA) for extended statistical analysis.

The GME removal efficacy was based on the following equations:

$$\text{GME volume (V) removal efficacy (\%):} \quad (1)$$

$$(1 - [\sum V \text{ after}]/[\sum V \text{ before}]) * 100$$

$$\text{GME count (C) removal efficacy (\%):} \quad (2)$$

$$(1 - [\sum C \text{ after}]/[\sum C \text{ before}]) * 100$$

The removal efficacy was defined as the accumulated relative ratio of volume (Eq. [1]) and counts (Eq. [2]) of GME within the measuring range (10–250  $\mu\text{m}$ ) after and before the oxygenator.

### Statistical Analysis

Results of bubble measurements were categorized according to GME size into 10 equal groups within the measuring range (10–250  $\mu\text{m}$ ). Descriptive statistics of GME count and volume characteristics were performed to illustrate intergroup differences. Differences between groups were analyzed by calculating the area under the curve (AUC) or by the predefined removal efficacy indices. Statistical tests were applied according to the distribution of data verified by plots. In the case of a normal distribution, either the 95% confidence interval or the Student's *t* test was applied; otherwise, the Mann-Whitney *U* test was applied. Results are presented as means  $\pm$  standard deviation. A *p* value  $\leq .05$  was considered statistically significant. Statistical analysis was performed using SPSS Version 18 (IBM Corporation, New York, NY) software.

## RESULTS

### Removal Efficacy of Gaseous Microemboli

The volume-based GME removal efficacy at 4 L/min pump flow rate reached 99.1%  $\pm$  .1% in the study group and 98.0%  $\pm$  .1% in the control group (*p* < .001), respectively. The removal efficacy of GME with reference to counts was 89.6%  $\pm$  .6% in the study group and 91.4%  $\pm$  .4% in the control group (*p* < .001). Details of results including the removal efficacy indices at 6 L/min pump flow rate are outlined in Table 1.

### Distribution of Gaseous Microemboli

The distribution of GME signified by counts and volume is presented in Figures 2 and 3. The volume and

**Table 1.** GME removal efficacy for counts and volume determined at low and high pump flow rates, respectively.\*

Low Pump Flow Rate (4 L/min)				
Removal Efficacy	Study	95% CI	Control	95% CI
GME count (%)	89.6 $\pm$ .6 <sup>†</sup>	89.2–90.0	91.4 $\pm$ .4	91.0–91.7
GME volume (%)	99.1 $\pm$ .1 <sup>†</sup>	99.0–99.1	98.0 $\pm$ .1	97.9–98.1
High Pump Flow Rate (6 L/min)				
Removal Efficacy	Study	95% CI	Control	95% CI
GME count (%)	55.6 $\pm$ 1.6 <sup>†</sup>	55.4–56.8	76.0 $\pm$ 1.4	75.0–77.0
GME volume (%)	97.9 $\pm$ .1 <sup>†</sup>	97.9–98.0	97.0 $\pm$ .4	96.7–97.3

\*Results denote means  $\pm$  standard deviation.

<sup>†</sup>*p* < .05 compared with the control group.

GME, gaseous microemboli; CI, confidence interval.

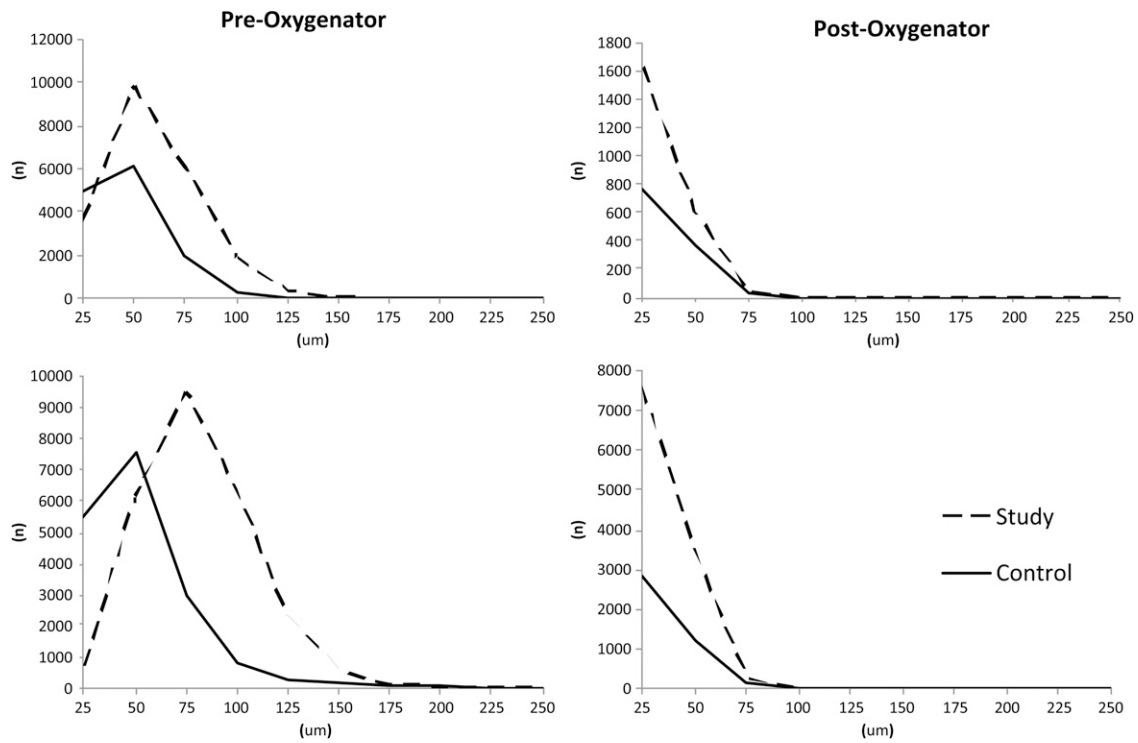
counts of GME as determined by the AUC were significantly higher in the study group compared with the control (*p* < .001), both for GME entering and leaving the oxygenator. These differences between groups were significant (*p* < .001), both at low and high pump flow settings.

The GME spectrum of counts entering the oxygenator reached was generally smaller than 175  $\mu\text{m}$  in size with a clear definable peak at 50–75  $\mu\text{m}$ . After oxygenator passage, there were hardly any identifiable GME counts larger than 75  $\mu\text{m}$ . The spillover of GME >75  $\mu\text{m}$  was .19% in the study group compared with .22% (*p* = .155) in the control group at the low flow rate setting. When increasing the flow rate to 6 L/min, the spillover was higher in the study group: 1.2% versus .7% in the control group (*p* < .001) (Figure 2).

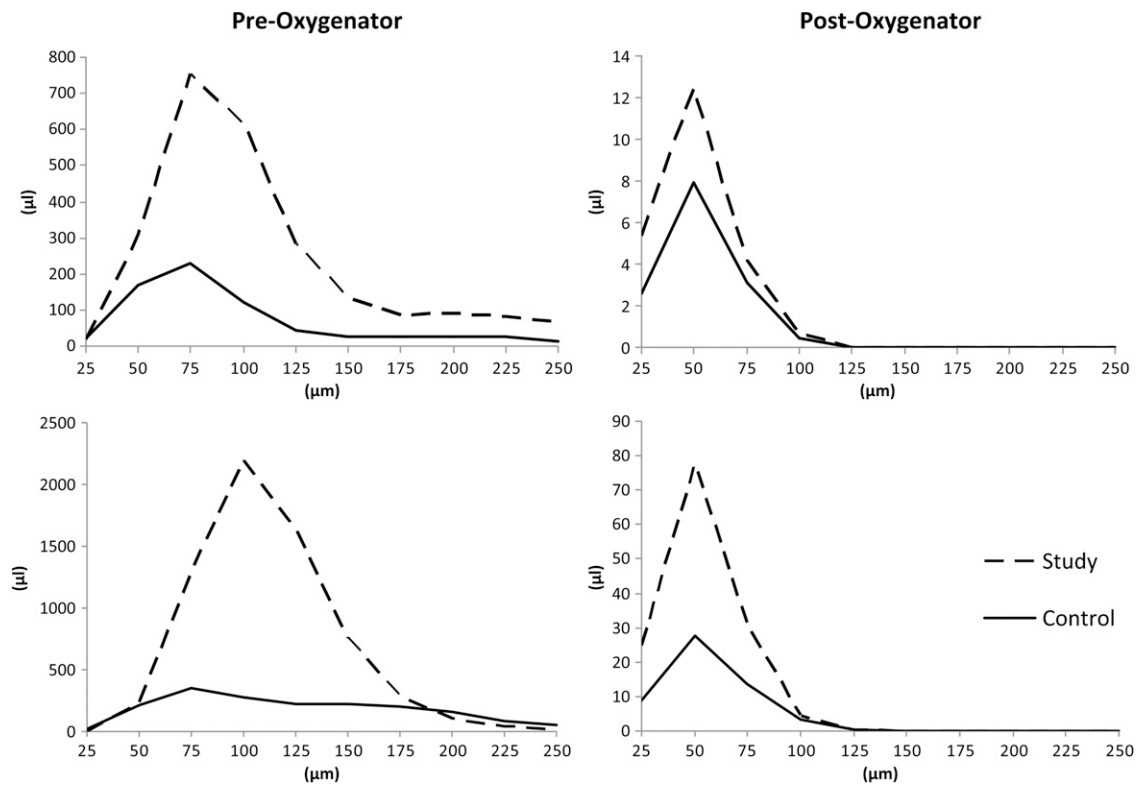
The GME spectrum signified by volume demonstrated a similar pattern as described for counts (Figures 2–3). However, the spectrum spanned over the whole measuring range (25–250  $\mu\text{m}$ ), the majority sized 75–100  $\mu\text{m}$  at entrance, decreasing in size to 50  $\mu\text{m}$  after oxygenator passage. The spillover of GME >100  $\mu\text{m}$  was throughout significantly lower in the study group: .2% versus .49% (*p* < .001) for the low flow rate and .54% versus .95% (*p* < .001) for the high flow setting.

## DISCUSSION

Screen filtration made the oxygenator significantly more effective in reducing the embolic load; i.e., based on the calculated volume of GME >100  $\mu\text{m}$ . The GME reduction was evident regardless of pump rate setting. At the same time, the filter was associated with an overall less effective GME count reduction, especially at high flow rates. Counts of GME >75  $\mu\text{m}$  were generally effectively blocked by the oxygenator itself, whereas the screen filter tended to split bubbles and increase the number of the smallest-sized GME.



**Figure 2.** Size distribution of gaseous microemboli (GME) based on counts. Area curves of GME counts describing the size distribution from 25 to 250  $\mu\text{m}$  at the oxygenator's venous inlet (left panels) and arterial outlet (right panels). Upper panels refer to pump flow rate 4 L/min. Lower panels refer to pump flow rate 6 L/min.



**Figure 3.** Size distribution of gaseous microemboli (GME) based on volume. Area curves of GME volume describing the size distribution from 25 to 250  $\mu\text{m}$  at the oxygenator's venous inlet (left panels) and arterial outlet (right panels). Upper panels refer to pump flow rate 4 L/min. Lower panels refer to pump flow rate 6 L/min.

Use of CPB has in the literature been described to cause microembolization to the brain (11,12). Cerebral microemboli are believed to cause postoperative cognitive decline (POCD) (13). Fifty percent of the patient population is believed to suffer from POCD at discharge from the hospital, still present in 42% of the cohort 5 years later (2). More recent findings would indicate that development of POCD is multifactorial. In a systematic review undertaken by Kruis et al. (12), no certain causal relation link could be established between the use of CPB and the development of POCD. Regardless to what extent the use of CPB can be attributed to the development of POCD, all means of protective measures should be undertaken to protect the patient from GME exposure.

The use of arterial line filters has always played an important role, particularly in conjunction with bubble oxygenation to prevent arterial embolization and remains to date the recommended standard of practice (6). New concepts of oxygenator design have made it possible to reside the arterial filter inside the oxygenator housing. To the best of our knowledge, the FX oxygenator was the first oxygenator on the market with this functionality. The location of the filter may be associated with several theoretical advantages such as negligible additional priming volume and ease of deairing. Other manufacturers have implemented similar solutions. A new oxygenator design, in which the arterial filter is a component of the oxygenator, should reassess the need for conventional standalone arterial line filters (14). It should in this context be emphasized that the membrane oxygenator itself possesses potent GME-reducing properties, herein exemplified by the overall, near 98% embolic load reduction for the tested Capiox<sup>®</sup> RX 25.

Previous studies have shown that the design of the oxygenator itself is a crucial component of GME removal efficacy (15). The GME reduction is in theory based on variations in blood flow velocity combined with the transit time of blood being in contact with the microporous hollow fiber in the oxygenator (16). The transmembrane pressure drop and the composition of the ventilating sweep gas represent other components influencing the GME removal efficacy (9). Different brands of CPB circuits demonstrate therefore individual GME reduction properties, which underline the decisive aspects of circuit design in general (17). Our study was designed to evaluate the effect of arterial screen filtration per se. No efforts were made to evaluate other components of the experimental circuit with respect to GME removal properties. However, the circuit design was kept identical in both the control and study groups.

When examining an oxygenator's GME-reducing properties, some underlying physical mechanisms are of concern. One essential component is the bubble point pressure (BBP). The BBP may be used to calculate the effective

pore size of the filter screen. Factors that determine the BBP are the surface tension combined with its wetting angle in contact with the filter material and finally the filter's pore diameter. When the BPP exceeds the trans-filter pressure drop, the physical conditions are met for GME passage (14). In our experiment, we observed a tendency of large bubbles to split into smaller ones. The reason for this remains unclear. One may speculate the altered filterability caused by entrapment of GME combined with shear stresses may have played a role in producing smaller-sized bubbles.

One possible limitation of the present study refers to the quantification of embolic load. The pulsed Doppler technique used by the Gampt apparatus assumes spherical-shaped GME, whereas the actual shape may have been nonspherical as a result of influences of changes in velocity and shear forces. This theoretical reasoning may have been inferred with an accurate calculation of the embolic load (8,14). The Gampt BC200<sup>®</sup> was in a recent study compared with EDAC<sup>®</sup> (Luna Technologies, Blacksburg, VA), which uses fixed-beam ultrasonic imaging. The Gampt system was found to both under- and overestimate the bubble size depending on the actual flow setting, whereas the EDAC system consistently underestimated the bubble size diameter (8). However, in the present study, both groups were subjected to identical testing conditions using the same type of bubble monitor and methodology of data analysis.

Previous studies have indicated the GME filtration properties of the FX oxygenator to be comparable to standalone arterial line filtration (18–20). In accordance with our experimental data and verified clinically, the FX oxygenator appears to be superior to the RX in reducing the GME (21). However, it should be emphasized that all these results were obtained from pediatric perfusion, whereas data from the adult population in this respect remain sparse.

Both types of oxygenators were able to reduce a higher GME load than what we normally would expect in clinical practice. This may be explained by the blood analog used in this experiment, which is not identical to the gaseous binding properties of plasma. However, the same priming solution has previously been considered appropriate (8,22). Moreover, only one oxygenator in each group was used. A larger sample of oxygenators would have been preferred. The detected differences between groups, with respect to premembrane GME load, may add further criticism and suggest unequal intergroup test conditions. However, it should be emphasized that the size of GME was approximately evenly size distributed within groups and that the statistically verified differences between groups were based on the results of both pre- and postmembrane conditions. Hence, despite the difference in oxygenator GME input, possibly favoring the

control group with a lower provocation level, similar patterns of efficacy were observed in both tested oxygenators. In the clinical setting, the GME size pattern is typically diverse with substantial variations in GME load, both with respect to size and volume (18,21). To date, no general consensus exists with respect to the arterial line filter's GME reduction capacity. Test conditions are warranted, in which GME standards can be established. Such standards are of interest not only for arterial line filters, but also for filters in general, including standards for oxygenators and reservoirs.

The scientific evidence we have today for using arterial filters goes back to publications made more than 20 years ago (6). Relevant high-quality clinical trials describing the existing standard of extracorporeal circulation with reference to arterial filtration are lacking (14). Despite these apparent drawbacks, use of arterial filters is the current recommended standard based on the highest level of scientific evidence: Class I, Level A (6). Further investigations addressing the need for arterial filters in conjunction with extracorporeal circulation are urgently needed. What we have described in this pilot experiment indicates that the overall filterability seems to be good, including both the membrane of the oxygenator itself, but also the additive GME removal effect gained by the addition of the arterial screen filter. The latter effect is very small but, nevertheless, statistically justified. What clinical impact these findings would have on patient outcome is unfortunately at present limited to speculation. Of interest is that a great majority of cardiac units in Sweden do not advocate the use of arterial line filters, which means that a huge population of patients over the years has been exposed to CPB without arterial filtration, apparently with good clinical results. The scientific value of a remark of this kind is of course very limited, but the everyday "clinical eye" is a source of information, which cannot be neglected. Moreover, the design of new extracorporeal membrane oxygenation (ECMO) circuits does not include arterial filters, which seems to be a generally accepted standard. What should be underlined is that the ECMO treatment situation differs. The risk of GME is probably less pronounced compared with CPB, however, still existing.

The ideal CPB circuit does not yet exist. However, with adoptions of new technologies intended for prevention of venous air entrainment (23), elimination of gaseous and particulate emboli in the blood entering the oxygenator and an oxygenator-integrated arterial filter would improve the quality of CPB. Large-scale studies including complete monitoring of gaseous entry, transformation and distribution from the CPB circuit into the patient arterial vasculature, combined with postoperative psychometric tests are warranted. The role of CPB as a cause for POCD is still a matter of concern (12,24).

## CONCLUSION

The tested oxygenator, with a novel incorporated arterial filter screen, did decrease the embolic load expelled from the oxygenator, however, at the expense of an increasing number of GME. On the other hand, the oxygenator without a filter revealed almost similar GME scavenging properties. The clinical benefit from adding an arterial screen filter needs to be addressed in future trials.

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