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ORIGINAL ARTICLE

Clinical evaluation of the air removal characteristics of an oxygenator with integrated arterial filter in a minimized extracorporeal circuit

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ABSTRACT

The use of minimized extracorporeal circuits (MECC) in cardiac surgery is an important measure to increase the biocompatibility of cardiopulmonary bypass during coronary artery bypass grafting (CABG). These circuits eliminate volume storage reservoirs and bubble traps to minimize the circuit. However, the reduction in volume may increase the risk of gaseous microemboli (GME). The MECC system as used by our group consists of a venous bubble trap, centrifugal pump, and an oxygenator. To further reduce the risk of introducing GME, an oxygenator with an integrated arterial filter was developed based on the concept of minimal volume and foreign surface. We studied the air removal characteristics of this oxygenator with and without integrated arterial filter. The quantity and volume of GME were measured with precision at both the inlet and outlet of the devices.

Our results showed that integration of an arterial filter into this oxygenator increased GME reducing capacity from 69.2% to 92%. Moreover, we were able to obtain data on the impact of an arterial filter on the exact size-distribution of GME entering the arterial line.

The present study demonstrates that an MECC system and oxygenator with integrated arterial filter significantly reduces the volume and size of GME. The use of an integrated arterial filter in an MECC system may protect the patient from the deleterious effects of CPB and may further improve patient safety.

KEY WORDS: *Cardiopulmonary bypass, Minimized extracorporeal circuits, Arterial filter, Gaseous microemboli, Safety*

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INTRODUCTION

Cannulation, drug administration, blood sampling, and various components of the cardiopulmonary bypass (CPB) circuit are potential sources of gaseous microemboli (GME) during on-pump cardiac surgery (1-3). Introduction of GME into the arterial line of a CPB circuit may lead to cognitive decline and adverse outcomes (4, 5). Arterial filters are incorporated into conventional bypass circuits as a safeguard for gross air and may reduce the number of GME measured in the arterial line (6, 7). A 40 µm arterial filter reduces the number of GME by 50% to 73%, depending on the GME diameter (8). Gerriets et al (9) even demonstrated a neuroprotective effect by using an arterial filter.

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Miniaturized extracorporeal circuits (MECC) have been developed to reduce both blood contact surface area and priming volume. In this development process, air removal components of the CPB circuit such as venous reservoirs and even arterial filters have been omitted. In the event of accidental gross air introduction, there may be the risk of less efficient air handling in a closed loop system as compared to conventional systems (10). Accordingly, a venous bubble trap (VBT) with minimal priming volume (160 mL) was developed. This VBT scavenges gaseous macroemboli (> 500 μm) almost completely (11) and was therefore incorporated into our MECC system for daily use in order to improve patient safety.

A newly developed oxygenator with an integrated arterial filter reduces surface area and priming volume even further while maintaining circuit simplicity. Now the question arises if integration of this arterial filter in combination with a VBT has additional value in reducing microemboli. The aim of this study was thus to assess the air removal characteristics of this new oxygenator compared to the same oxygenator without integrated arterial filter in a MECC system during coronary bypass graft surgery (CABG) by measuring number, size, and total volume of GME.

MATERIALS AND METHODS

Patients

A prospective randomized study was performed in a teaching hospital in Nieuwegein, The Netherlands. After approval from the local Medical Ethics Committee, twenty patients undergoing elective revascularization with MECC were alternately assigned to be perfused either using an oxygenator with arterial filter (Oxygenator+AF group) or without an integrated arterial filter (Oxygenator group).

Included were patients undergoing first-time CABG with two- or three-vessel coronary artery disease. Excluded were patients undergoing emergency surgery, patients with combined surgical procedures, or when air was visually observed in the venous line during the procedure.

The MECC system

All the components of the system were purchased from Maquet, Hirrlingen, Germany. The closed loop MECC system was controlled by an HL30® heart-lung machine and consisted of a tip-to-tip heparin-coated tubing system (Bioline®). In the venous line a Venous Bubble Trap® (VBT) was integrated and blood flow was created with a centrifugal pump (Rotaflow®). In the Oxygenator group a Quadrox-i Adult® and in the Oxygenator+AF group a Quadrox-i Adult® with integrated arterial filter was used. The aortic vent line ran through a drip chamber and was connected to the VBT. During extracorporeal circulation, the recirculation line on the oxygenator or on the integrated arterial filter leading to the sample manifold was constantly open.

The MECC system was primed with either 650 mL (Oxygenator group) or 765 mL (Oxygenator+AF group). Priming solution was a combination of 500 mL of Haes 6% (Voluven®, Fresenius Kabi, Hertogenbosch, Netherlands) and 3 L of NaCl 0.9% (B. Braun, Melsungen, Germany). A level detector was located on the drip chamber in the aortic vent line and a bubble sensor (detection limit ≥ 5 mm) on the venous line. When a low level alarm occurred or air was detected, the centrifugal pump would stop.

Quadrox-i Adult® with and without integrated arterial filter

The Quadrox-i is an oxygenator and heat exchanger equipped with a microporous membrane. The priming volume is 215 mL. The Quadrox-i with integrated arterial filter has a priming volume of 330 mL. The integrated arterial filter is comprised of 4.5 parallel filter cassettes with a pore size of 40 μm. After diffusing through the filter medium, the blood flows through the individual cassettes towards the common outlet, which is located at the bottom of the housing. The integrated filter approach leads to a minimized priming volume, less blood foreign surface contact, and a more compact design.

CPB procedure

Anesthesia was induced by infusion of midazolam (0.02-0.1 mg/kg) in combination with propofol (0.5-2 mg/kg), pancuronium (0.1 mg/kg) and fentanyl (5-10 μg/kg). Anesthesia was maintained with a continuous propofol infusion (2-8 mg/kg per hour) and remifentanil (5-20 μg/kg per hour).

After heparinization (150 IU/kg) the aorta was cannulated with a Jostra® arterial 24 F cannula (Maquet, Hirrlingen, Germany). The right atrial appendage was cannulated with

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a Jostra® venous SLIM 32/37 F cannula (Maquet, Hirrlingen, Germany). The venous cannula was tied with a secondary snare in order to ensure an "air tight" cannulation site. A 7 F venting needle (DLP®; Medtronic, Minneapolis, MN, USA) was placed in the aortic root.

CPB was initiated when the ACT was 300 seconds, measured by a Hemochron® Jr (International Technidyne Corp. (ITC), Edison, NJ, USA).

During CPB, the nasopharyngeal temperature was maintained at 32°C to 34°C. After aortic cross-clamping, preservation of the heart was achieved by means of a modified Calafiore blood cardioplegia infusion (12). The initial dose of potassium was 5.7 mmol/min, and was followed by a second dose of 3.4 mmol/min after 20 minutes with subsequent doses of 2.6 mmol/min every 20 minutes.

During CPB the cardiac index was maintained at 2.4 l/min per m^2 and acid-base management was regulated according to the alpha-stat protocol. Mean blood pressure was maintained between 40 mmHg and 80 mmHg. After the initial blood cardioplegia dose and during rewarming, the pO_2 of blood samples were measured by a blood-gas analyzer (Rapidlab 855, Bayer, Tarrytown, NY, USA).

Shed blood was collected and processed with an autotransfusion device (Cobe Brat 2®; Sorin Biomedica SPA, Mirandola, Italy). After CPB, the residual blood in the MECC was rinsed with 1 L to 2 L priming solution and directed to the autotransfusion device. After CPB, heparin was neutralized with protamine sulphate at a 1:1 ratio.

Detection of gaseous micro emboli

GME were detected with a BCC 200 bubble counter (GAMPT mbH, Zappendorf, Germany). The measurements were conducted with two non-invasive sensor probes clamped on the 3/8 inch tubing. The probes were clamped on the inflow and outflow tubing of the oxygenator. The measurement is based on a self-calibrating ultrasonic Doppler device. The BCC 200 device measures accurately the number and the size of GME with a diameter ranging from 20 µm to 500 µm. The device identifies the bubbles with a diameter of more than 500 µm as "over range". Particulate emboli do not influence the count results. Data were collected and cumulated during the entire CPB procedure. To avoid measurement of electronic distortion produced by diathermal coagulation, an electronic filter algorithm was used.

Statistical analysis

Quantitative variables are presented as mean ± standard deviation (SD), when appropriate, unless otherwise stated. Normal distribution of the quantitative variables was assessed visually. Continuous variables were compared by means of Student's t-test or Mann-Whitney and Wilcoxon tests when appropriate. Categorical variables were compared by means of the Chi-square test.

A 95% cut-off value, introduced by us, was defined as the smallest diameter of GME, where 95 % reduction was observed. % Reduction is calculated by the formula:

$$\% \text{ Reduction} = [1\text{-}GME_{out}/GME_{in}]*100$$

Statistical analysis was performed using SPSS 10.0 (SPSS, Chicago, IL, USA).

RESULTS

Demographic and intra-operative data are summarized in Table I. There were no significant differences between the groups. One patient from the Oxygenator+AF group was excluded because of massive air entering the system through the venous line. The air was evacuated through the VBT air filter and the procedure was completed without complications. The patient was replaced to keep sample size equal. No air incidents took place in the other patients and all patients were discharged without neurological complications.

The GME-related data for both groups are listed in Table II. Within-group analysis demonstrated a significant decrease behind both oxygenator-devices in number of GME, the GME volume, and the range in number of "over range" bubbles. Only the number of GME normalized for CPB time was not significantly decreased in the oxygenator in contrast with the oxygenator with integrated filter. In all three micro emboli ranges, including number of GME normalized for CPB time, no difference was found between the groups considering GME entering the oxygenators. Both number of GME and number of GME normalized for CPB time showed no significant difference between both devices. The GME volume behind the oxygenator with arterial filter (3.1±3.0) was marginally lower (p=0.052) than in the oxygenator group (7.8±8.1). No significant difference was found between the number of 'over range' bubbles behind the oxygenator (0.1±0.32) or the oxygenator with integrated filter (4.1±12.6).

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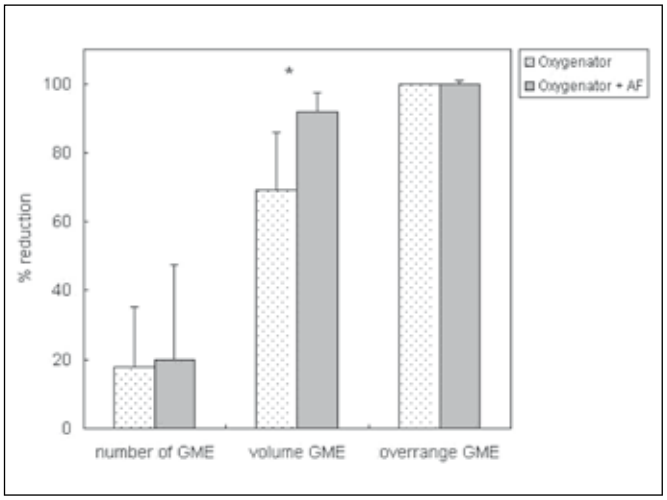

Fig. 1 - *Reduction of GME (%) in the Oxygenator and Oxygenator+AF group (data are presented as means ± SD).*

The mean % reduction is presented in Figure 1. The reduction of the number of GME was equal in both groups, 17.9 ± 17.3% in the Oxygenator group and 19.8 ± 27.7% in the Oxygenator+AF group (p=0.44). The reduction of the GME-volume of the Oxygenator+AF group was significantly better than in the Oxygenator group (92.0±5.3 vs. 69.2±16.6, p=0.002). "Over range" GME were almost completely eliminated in both the Oxygenator and the Oxygenator+AF group, respectively, by 100% and 99.7%.

Figure 2 shows that the size distribution of the number of GME entering both devices seems rather similar. However, the distribution of the number of microemboli leaving both devices reveals differences. The volume distribution curve could be calculated as shown in Figure 3 from the number of GME and their diameter. The distribution of the GME volume in both groups shows more detail about the GME entering (in) and leaving (out) the devices.

To make interpretation of the data more clear, the % reduction per GME size is shown in Figure 4. In the Oxygenator group, rather than being reduced, GME from 20 µm to circa 160 µm were apparently generated. In the Oxygenator+AF group, the same phenomenon was observed with GME from 20 µm to circa 90 µm.

The 95% cut-off for the Oxygenator group was 318 µm and for the Oxygenator+AF group 165 µm.

TABLE I - DEMOGRAPHIC AND INTRAOPERATIVE DATA

	Oxygenator group	Oxygenator+AF group	*P* value
n	10	10	n.s.
Age (y)	67±7	62±9	n.s.
Female sex (%; n)	20 ; 2	20 ; 2	n.s.
BSA (m^2)	1.96±0.21	1.99±0.21	n.s.
CPB time (min)	83±16	98±32	n.s.
Cross-clamp time (min)	53±13	64±23	n.s.
Distal anastomoses (n)	4.2±1.2	4.3±1.2	n.s.
Mean pO_2 (mmHg)	22.5±5.7	22.5±6.4	n.s.
Minimal blood temperature (°C)	34.1±0.6	34.4±0.2	n.s.

Data are presented as means ± SD, except for sex (%); BSA = body surface area; CPB time = duration of cardiopulmonary bypass; n.s. = non-significant.

TABLE II - RESULTS OF GME MEASUREMENT IN THE OXYGENATOR AND OXYGENATOR+AF GROUPS

	Oxygenator			Oxygenator + AF		
	In	Out	*P* value (*)	In	Out	*P* value (*)
Number of GME (20-500 µm)	9806±5420	7893±4553	0.0098	12306±11018	9653±8996	0.0273
Number of GME/CPB time (n/min)	100±53	91±49	0.0839	132±16	93±53	0.0039
GME volume (µL)(20-500 µm)	25.4±14.2	7.8±8.1	0.0020	35.5±26.3	3.1±3.0	0.0020
Number of "over range" bubbles (n)	97.0±72.0	0.1±0.3	0.0020	168.2±163.2	4.1±12.6	0.0190

Data are presented as means ± SD; CPB time = duration of cardiopulmonary bypass; * = Wilcoxon test.

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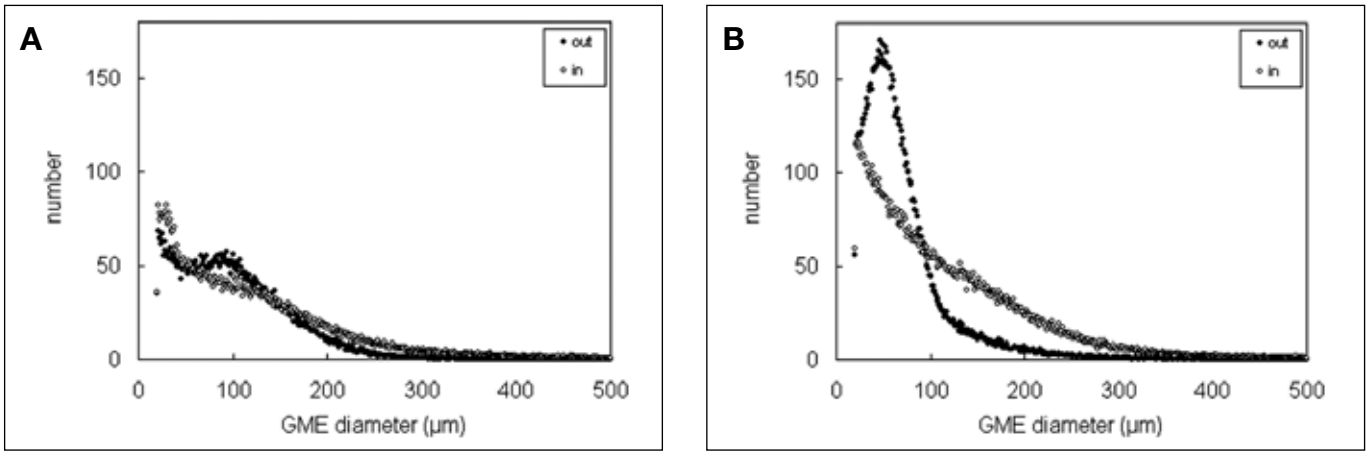

Fig. 2 - *Distribution of number of GME (20-500 µm).* ***A:*** *Oxygenator;* ***B:*** *Oxygenator+AF (data are presented as means).*

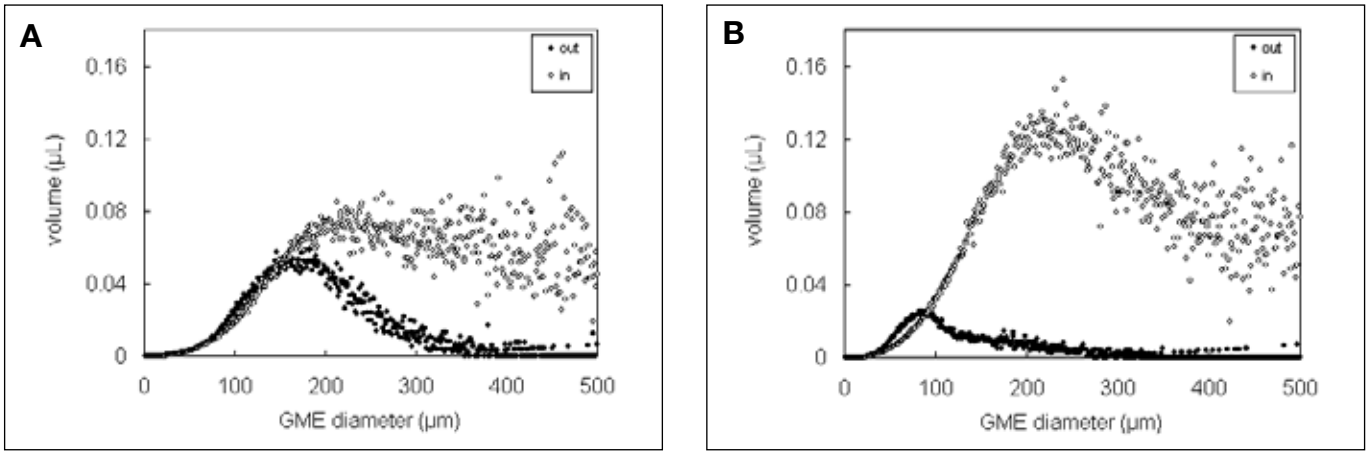

Fig. 3 - *Distribution of GME volume (20-500 µm).* ***A:*** *Oxygenator;* ***B:*** *Oxygenator+AF (data are presented as means).*

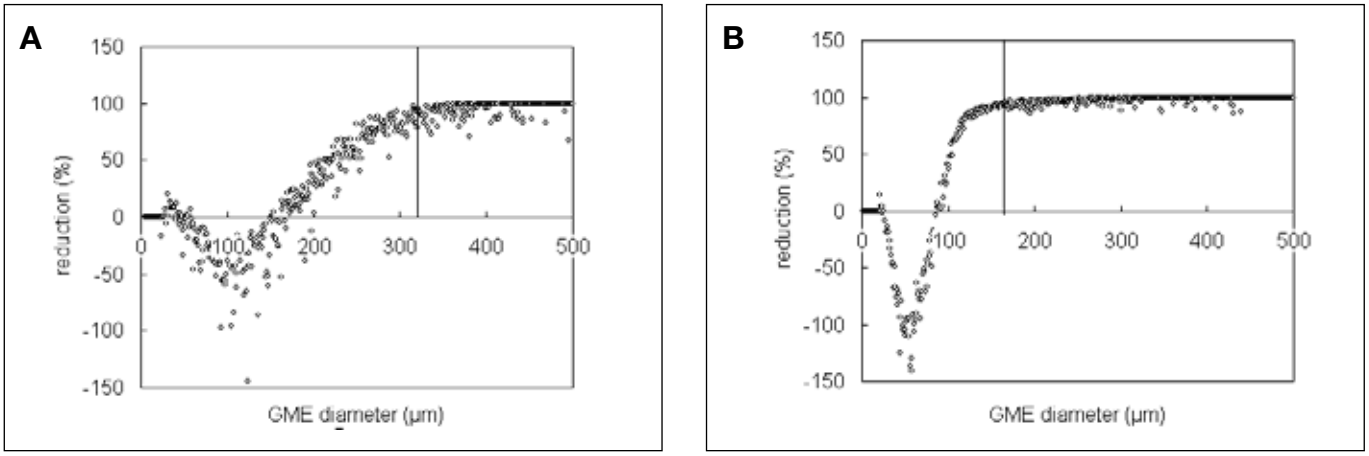

Fig. 4 - *Relation between reduction and GME size (the 95% cut-off value is shown as vertical lines).* ***A:*** *Oxygenator;* ***B:*** *Oxygenator+AF (data are presented as means).*

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DISCUSSION

Both the oxygenator with and without integrated arterial filter reduced the volume of GME and "over range" bubbles. In addition, integration of an arterial filter in an oxygenator led to a more significant reduction in both size and volume of GME as compared to a oxygenator without arterial filter. Moreover, thanks to the use of a new-generation bubble counter that accurately quantifies and qualifies GME, we were able to gain insight from detailed GME distribution data. For the first time we were able to visualize the impact of an arterial filter on the exact size-distribution of GME entering the aortic line and subsequently contributing to the embolic load of the patient.

Originally, the MECC system consisted only of a centrifugal pump and an oxygenator (13, 14). With this MECC system, a reduction in priming volume of approximately 600 mL was obtained as compared to a conventional ECC system with a priming volume of 1500 mL to 2000 mL. The combined efforts of warm blood cardioplegia, transfusion of processed shed mediastinal blood, a reduction of blood-air contact, and decreased foreign surface contact may lead to an improved clinical outcome after cardiothoracic surgery (15).

Despite the lack of air removal components, various studies showed that during CPB the number of gaseous emboli entering the patient decreased when compared to conventional CPB (16, 17). This could either be caused by the totally closed aspect of the MECC system, or by the lower initial air entrapment in the venous line during connection of the mini-system (18).

A closed loop system, as in mini systems, may be more vulnerable to accidental gross air introduction (10, 13, 19). For this reason, a VBT was developed as a safety device. A recent study (11) from our group showed that a VBT in a MECC system reduced the volume of GME (20-500 µm) by 71%. "Over range" GME were scavenged for 97% by this venous filter.

Our results showed that although our current MECC system is equipped with a VBT, GME were still able to reach the oxygenator devices. We showed that integration of an arterial filter into this oxygenator increased GME reducing capacity from 69.2% to 92%.

Two recent *in vitro* studies showed corresponding GME reduction rates of 89% to 95% by the same oxygenator with integrated arterial filter (20), or by a combination of the oxygenator with a separate arterial filter (21). Recently, Jirschik et al (22) observed a comparable GME volume reduction of 75% with the use of this oxygenator without an integrated arterial filter. However, the reduction of number of GME in the oxygenator with arterial filter was 17.9%, while the GME volume reduction was 92%. This may be explained by the phenomenon that GME can be fractionated into a higher number of smaller GME. This explanation is supported by a recent study, which showed that GME entering the MECC system also appeared in the arterial outflow and were only fractionated into a higher number of smaller GME without reduction of the total volume (23). This fractionation phenomenon can be observed in our graphs showing obtained distribution of volume and percentage reduction. In the percentage reduction graphs especially, the "generation" of small GME is visualized by the negative reduction rates as found in the smaller GME diameter range. Therefore, in our opinio, measuring GME volume instead of number of GME is of additional value.

Also, using the number of GME normalized per CPB time is not a reliable parameter in our opinion because of this fractionation of GME, and also the cause of GME generation during CPB. GME generation during CABG seems to be correlated to perfusionist interventions rather than to surgical interventions (2, 3). This can result in longer CPB times caused by surgical technique while no more perfusionist interventions occur.

Interpretation of our data based on detailed reduction characteristics made it possible to introduce a new parameter, the 95% cut-off value. The 95% cut-off value was defined as the smallest diameter of GME where 95% reduction was observed. The cut-off for the oxygenator group without integrated arterial filter was 318 µm and for the oxygenator group with integrated arterial filter it was 165 µm. Although the size of GME causing pathological changes is not known, bigger GME may be prone to worsen ischemic damage. GME can block small arteries, sized 30 µm to 60 µm (4). Their dissolution time increases with bubble size According to a formula (24) based on theoretical and experimental results, GME with diameters of 318 µm and 165 µm will be absorbed in approximately 47 min and 12.5 min, respectively. This means that the integrated arterial filter is able to reduce the ischemia time caused by GME by approximately 35 minutes.

The GME size distribution graphs also showed different characteristics of the GME entering the two devices. This may be explained by the fact that the oxygenator with integrated arterial filter reduces the number of the GME more

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efficiently, thus possibly resulting in more GME re-entering the venous side of the MECC circuit through the recirculation line on the oxygenator.
Gerriets et al (9) showed that a complex and multifactorial problem like postoperative cognitive decline after 3 months could be improved by the use of an arterial filter. Our results show that this may be merely an effect of decreased bubble size as caused by an arterial filter than reduction of total bubble volume. Besides the possible negative effect of GME on cognitive functioning, GME may induce an inflammatory response and may damage endothelial cells, leading to ischemia injury of end-organs (5). Therefore, reducing size and volume of GME by an arterial filter may contribute to the protection of the cardiac patient against the adverse effects of CPB.
The advantage of decreased hemodilution as obtained with MECC may contribute to better organ protection, improved neurological outcome (25, 26) and a reduction in the number of blood transfusions (13, 14, 27). Compared with the original MECC system (circa 600 mL), the addition of both the VBT (160 mL) and the integrated arterial filter (115 mL) will lead to a total priming volume of circa 875 mL. Although we do not know the effect of slightly higher hemodilution on outcome, we argue that the reduction of GME size (95% cut-off) entering the circulation could justify the use of an arterial filter.

Limitations

This study has some limitations. Caution should be taken when detailed bubble distribution is used. We are aware that the measurement error for the GME diameter is not known; we interpreted the measurement error as random noise, as seen in the distribution graphs, and concluded that this does not invalidate our computations or ensuing inferences since the precision alone was impaired.
The BCC200 calculates the GME volume on the hypothesis that the bubble is a perfect sphere. Especially with increased diameters this hypothesis becomes less and less true and may result in impaired precision.
De Somer et al (28) showed that the BCC200 bubble counter overestimates sizes of micro bubbles by more than 200%. However, one limitation of their study was that only one apparatus was tested and the study was not carried out in routine care of the patient but, rather, during a worst-case scenario, namely, high embolic loads. The concentration of bubbles was probably too high since the BCC200 is limited to measuring no more than 200 bubbles per second as mentioned in a comment of Schultz et al (29).
Nevertheless, the article by De Somer et al raises concerns about the validation of bubble counter devices and stresses the need for independent research on GME validation.

CONCLUSIONS

Both the oxygenator with and without integrated arterial filter reduced the volume of GME significantly, although the oxygenator with integrated arterial filter reduced the volume of GME more than the oxygenator without integrated arterial filter. In both groups the “over range” bubbles were almost completely removed by the devices.
An arterial filter may protect the patient from the deleterious effects of GME by reducing both the volume and the size of GME, which contribute to the embolic load. Therefore, the use of an integrated arterial filter during CABG with a MECC could be justified.
An important secondary conclusion is that with the aid of the new-generation bubble counters, detailed GME distributions can be obtained. The use of GME volume instead of number of GME provides more detailed information on the reducing characteristics of CPB circuit components, but awaits empirical evidence on clinical relevance.

Conflict of interest statement: The authors declare that there are no conflicts of interest in relation to this scientific work.

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