

Original Articles

Gaseous Microemboli and the Influence of Microporous Membrane Oxygenators

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Abstract: Gaseous microemboli (GME) are still an unsolved problem of extracorporeal circuits. They are associated with organ injury during cardiopulmonary bypass. Microbubbles of different sizes and number are generated in the blood as the result of different components of the extracorporeal circuit as well as surgical maneuvers. The aim of our study was to observe the behavior of microporous membrane oxygenators to GME in the daily use and in an in vitro model. For the detection of microbubbles, we used a two-channel ultrasonic bubble counter based on 2-MHz Doppler-System with special ultrasound probes. The amount and size of GME were monitored before

and after membrane. In 28 scheduled cases with 3 different oxygenators and variability of surgical procedures, we observed the bubble activity in the extracorporeal circuit. In addition, we used an in-vitro model to study the ability of six different oxygenators by removing air in various tests. The oxygenators tested were manufactured with different membrane technologies. The results of our investigations showed varying membrane design lead to a partial removal of GME as well as a change in size and numbers of microbubbles. **Keywords:** gaseous microemboli, extracorporeal circuit, membrane oxygenators. *JECT. 2005;37:256-264*

Since the early days of cardiopulmonary bypass (CPB), with all accessories needed to perform extracorporeal perfusion, the presence of gaseous microemboli (GME) has been an unsolved problem (1). Recent studies demonstrated the phenomena of brain embolism, which is associated with cardiopulmonary bypass (2). Brain embolism leads to postoperative organ dysfunction and neurologic complications. Despite the advances in surgical technique, anesthesia management, and CPB to reduce morbidity and mortality, the incidence of neurologic injury (2-5%) remains relatively high (3). The relationship between microemboli and the incidence of organ damage has been demonstrated (4). The origin of GME is multifactorial and

can be seen by surgical manipulation such as insertion and removal of the aortic cannula, vent and cardioplegia needle, aortic cross clamp and clamp removal; defibrillation; and other maneuvers. Fifty percent of cerebral emboli during CPB are not directly associated with surgical manipulation. Their origin is unclear. CPB-related sources of GME depend on the design and setup of extracorporeal circuits and the perfusionist attention conducting the bypass. There is no doubt that membrane oxygenators generate fewer GME than bubble oxygenators in the past. The design of the reservoirs influence the origin of GME as well as the blood level inside. High-flow suction, a pressurized cardiotomy reservoir (5), and inadvertent detachment of oxygenator during bypass are instances of massive air embolism. The function of the arterial filter as a trap for GME is definite by their specific pore size.

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Taylor et al. hypothesized that perfusionist interventions such as blood sampling and drug injections result in the majority of unexplained emboli (3), which was confirmed by Borger et al. (6). They proved that the introduc-

tion of air by perfusionist intervention may contribute to postoperative impairment (6). The use of level and bubble detectors in addition with arterial line filters or bubble trap may be protective in the face of massive air.

Bubbles introduced to the arterial circulation in patients undergoing CPB may have an impact in the cerebral circulation within seconds. Large bubbles ($>200\ \mu\text{m}$) may arrest in cerebral arterioles for variable periods causing ischemia and neuronal injury in the downstream territory. Smaller bubbles ($<15\ \mu\text{m}$) can pass through the microvasculature with little or no interruption of flow. Because of their high speed, smaller bubbles are able to strip off the endothelium from its basement membrane. Even small bubbles sizes of 10–20 μm compromise the blood–brain barrier.

Followed by the process of inflammatory response with perivascular edema and a decreased flow through microvasculature results in neurologic disorder. The magnitude and duration of ischemia determines the functional damage and is related to the volume of embolizing gas (7). Ultrasonography is the most common used method for detecting and counting microembolic events. This perioperative diagnostic monitoring includes transesophageal or periaortic echocardiography, transcranial Doppler, and fluorescing angiography (8).

The present measuring systems allows the detection of larger gaseous microbubbles and classification of the bubble size to roughly 10–15 μm . Some instruments has been criticized as causing multiple counting, movement artifacts, and unknown calibration (9). The purpose of our study was to investigate the GME reduction capability of different hollow fiber membrane oxygenators by using a new device that allows a permanent monitoring of the microbubble distribution in the blood flow in a range of 10 to 120 μm in diameter.

MATERIAL AND METHODS

This study was divided in an *in vivo* part, with three different membrane oxygenators in varying scheduled cardiac surgery procedures, and an *in vitro* part, with five different membrane oxygenators and a trial protocol of six tests. In the first group (*in vivo*), 28 patients (22 men and 6 women) undergoing cardiac surgery were assigned to three selected oxygenators: Affinity NT 511T oxygenator with Trillium coating (Medtronic Perfusion Systems, Minneapolis, MN), Biocor 200 oxygenator (Minnitech Corp., Minneapolis, MN), and Hilite 7000 oxygenator (Medos, Stolberg, Germany).

The surgical procedure included 14 coronary artery bypass grafting (CABG) with intermitted aortic-cross-clamping and 14 valve replacement (VR) with myocardial protection using Custodiol HTK cardioplegia solution (Köhler-Chemie, Alsbach, Germany).

Patient-relevant data were not considered in this study because we focused on the behavior of the used oxygenators in the reduction of GME. We used our standard “closed” heart–lung machine circuit consisting of a roller pump model HL20 (Jostra AG Hirrlingen, Germany), a polyvinylchloride (PVC) and silicon tubing set (Rehau, Rehau, Germany) with integrated, collapsible soft-shell venous reservoir, a hard-shell cardiotomy reservoir MC4040 (Medos Stollberg, Germany), and arterial line filter Affinity 351 arterial filter 38 μ (Medtronic Perfusion Systems) followed by a prebypass filter 2 μ (Sartorius, Göttingen, Germany).

The systems were flushed with CO_2 and primed with 2000 mL of Ringer’s lactate solution (Baxter, Unterschleißheim, Germany) added with 5000 IU heparin (Roche, Basel Switzerland). After carefully deairing and filling the system, the microbubble detection probes were placed 20 cm in front of the oxygenator (Figure 1) on the inlet tube and 20 cm behind the oxygenator on the outlet and connected via the users instruction manual with the UBC20 ultrasonic-bubble-counter (UBC; Figure 2; Converganza, Vaduz, Liechtenstein).

The distinctive feature of this device is the automated control of sensitivity to continuous measurement condition (ultrasound attenuation of the tube, coupling condition of the probe). The important difference of this device is the sensitivity and precision in contrast to other used systems. The UBC 20 identify microbubbles in their concrete size from 10 to 120 μm . Particles (blood elements, microthrombi) do not influence the measurement (10).

The two-channel construction, supported by specially designed software, allows the UBC to investigate changes in number and size distribution of bubbles in extracorporeal systems. It is possible for the user to evaluate the data

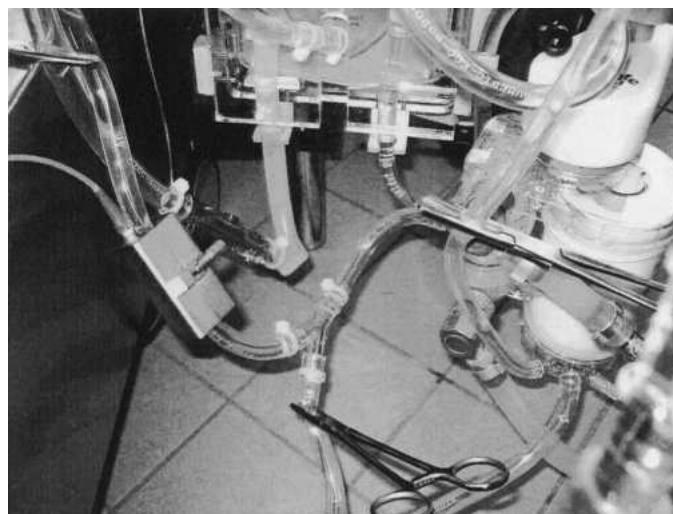


Figure 1. Bubble detection probe placed on the venous line of the circuit.

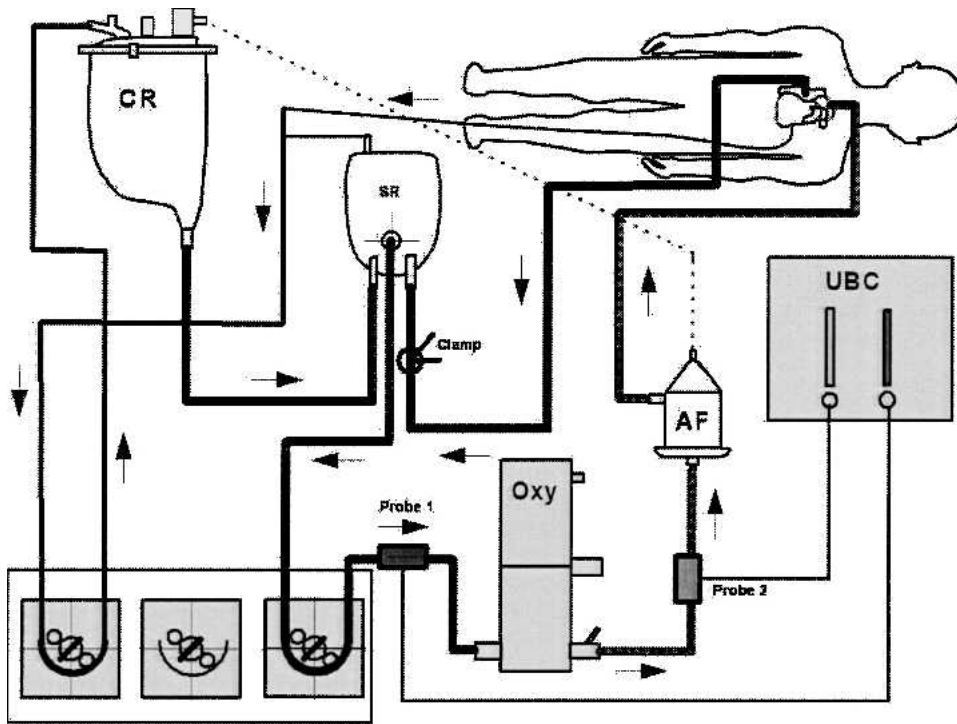


Figure 2. Diagram of the "closed" circuit for the in vivo study. Bubble detection probes were placed in front and behind the oxygenator.

after the investigation because this device records the raw data on a hard disk.

In our study, we detected simultaneous bubble activities in front and behind the chosen oxygenators. The efficiency of bubble reduction of membrane oxygenators was observed under in vivo conditions and with a special protocol of six tests for in vitro examination.

In the in vivo part of this study, bubble activity was recorded parallel by the perfusionist and the UBC in the moment bypass started until the end. Every event, including a surgical or perfusionist action, such as aortic cross-clamping, inserting the vent, or blood sampling, was the bubble-counter protocol.

Five different membrane oxygenators were selected for the in vitro study. The membranes used for all these oxygenators consist of microporous polypropylene hollow fibers. The blood flow outside the fiber with gas moving inside. Most of the oxygenators have a top-to-bottom blood flow orientation. The oxygenator-types differs in fiber construction. The single-strand technology was used in the Affinity and a wounded single-fiber-matt was seen in the Hilite, SafeMaxi, and Synthesis oxygenators. In the Quadrox and Biocor oxygenators, the fiber matt are laid cross-wise. The blood enters the venous port below the heat exchanger. After passing the heat-exchanger the blood flows downwards, more or less crossing the fiber bundles to the arterial outlet (Figure 3).

For the in vitro investigation we chose the following oxygenators: Affinity, Hilite 7000, SafeMaxi (Polystan, Vaerlöse, Denmark), Synthesis (Sorin Biomedica, Miran-

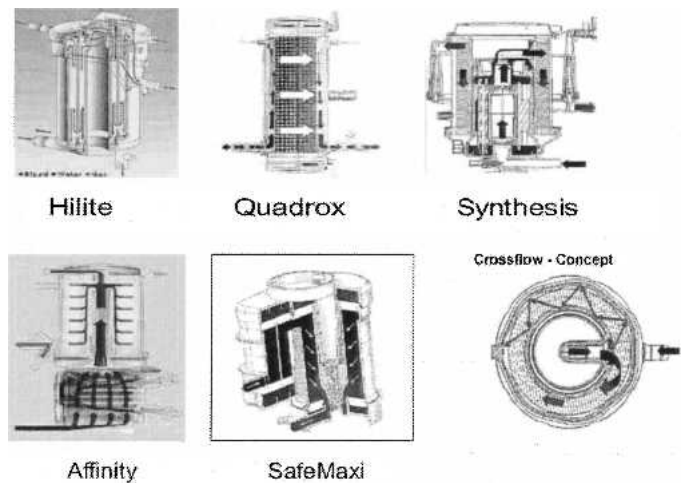


Figure 3. Cross-section of present membrane oxygenators with various flow patterns.

dola, Italy), and the Quadrox (Jostra, Hirrlingen, Germany).

Three oxygenators in this study were coated: the Affinity (Trillium), SafeMaxi (Safeline), and the Synthesis (Mimsys). Only the Quadrox oxygenator provides a hydrophobic membrane unit at the bottom of the venous side for de-airing. Considering that the Synthesis oxygenator includes an arterial filter unit with 40μ pore size, we placed the second bubble detection probe behind the arterial filter in all trials. For each trial in our in vitro study, we set up our standard circuit under sterile condition (Fig-

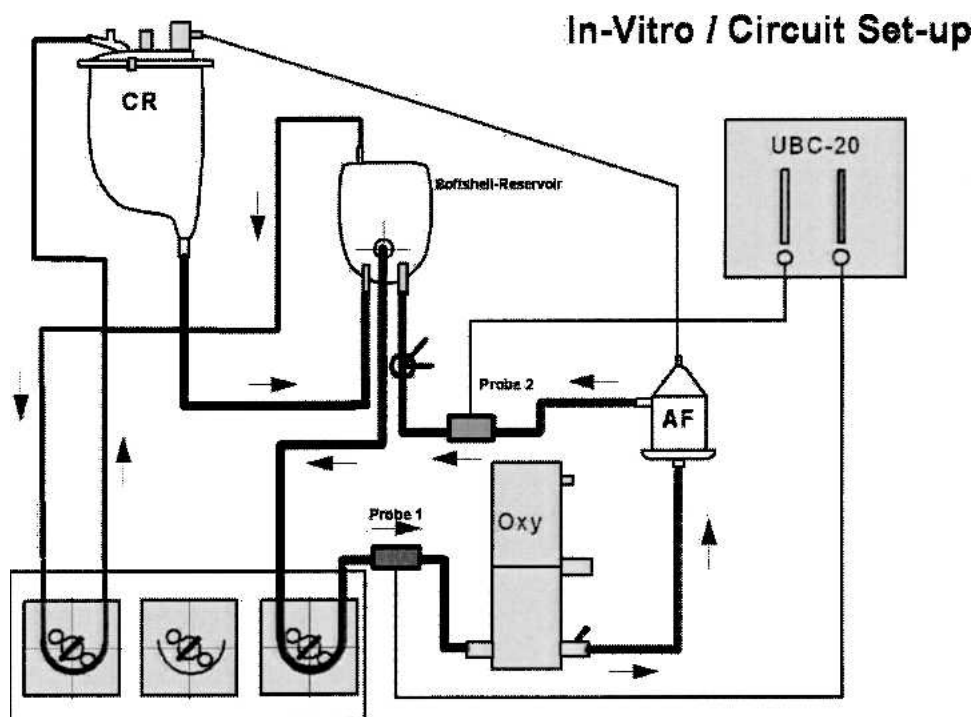


Figure 4. Circuit set-up of the in vitro trial.

ure 4). The system was flushed with CO_2 and primed as mentioned before. Temperature of the fluid was set to 37°C . by a heater-cooler unit HCU 20 (Jostra, Hirrlingen, Germany). While a steady-state flow of 4.5 L/min was maintained, a screw clamp was set on the outlet tube mimicking the gradient of the arterial line at 170 mmHg.

Each trial included six tests simulating the different situation of generating GME. For each test, the pump-flow was set to 4.5 L/min, the gas-flow 2.0 L/min, and the F_iO_2 at 50% for a recording time of 10 minutes. The first test simulated the recirculation period, including a prebypass-filter. The second test was conducted under the same circumstances noted previously. The level in the cardiomy-reservoir was set to 400 mL. A bolus air of 50 mL was injected by hand in the venous line.

In the third test, the reservoir was emptied. Here, we simulated the cascading effect of the reservoir, opening the purge-line of the arterial filter and the cardiomy sucker was started. 50 mL of air was injected in the soft-shell reservoir remaining for 2 minutes. After that the reservoir was deaired and the level of the cardiomy-reservoir was set to 400 mL.

In the fourth test, the crystalloid solution was exchanged by time expired acid citrate dextrose blood units to have a constant Hct. of 20%. The level in the reservoir was set at 1000 mL. 50 mL of air was injected in the venous line. After 3 minutes, the air in the soft-shell reservoir was eliminated by the coronary suction.

In the fifth test, a perfusor was started after 30 seconds, injecting air in the venous line at 50 mL/h. The sixth test

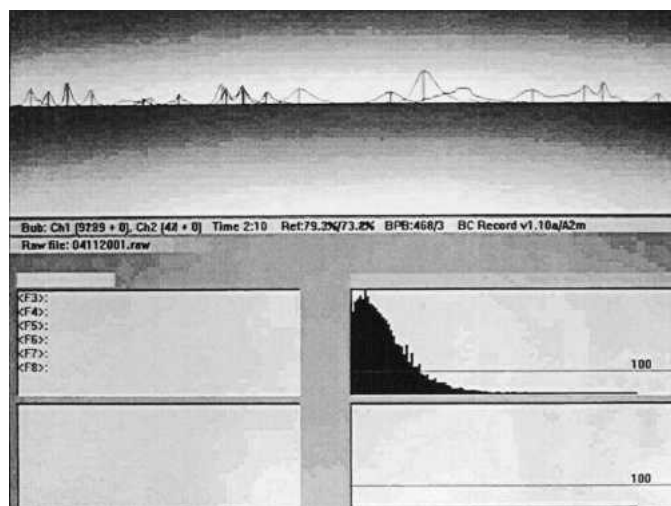


Figure 5. Recording of the bubble recorder monitor.

was nearly identical with the fifth test, but the volume of injected air was raised up to 100 mL/h. Bubble activity was recorded in each trial for 10 minutes (Figure 5)

Statistics were done by SPSS 11.0 for Windows (SPSS Institute, Chicago, IL). Data are expressed as mean and standard deviation.

RESULTS

In the in vivo group, we observed microbubble activity according to surgical or perfusion manipulation. There

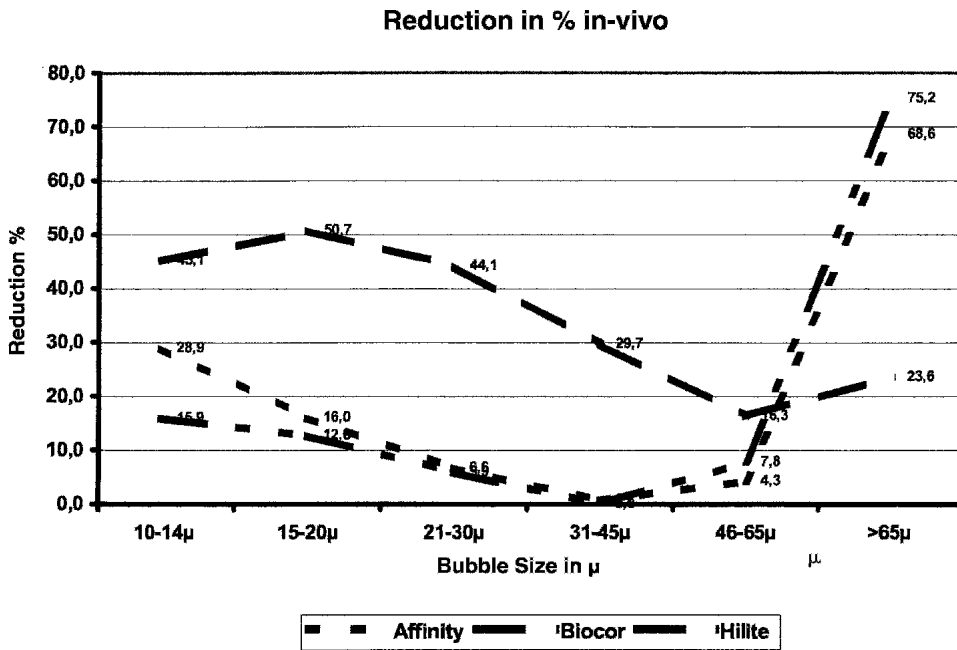


Figure 6. Reduction rate in percent of the in vivo group in relation to bubble size.

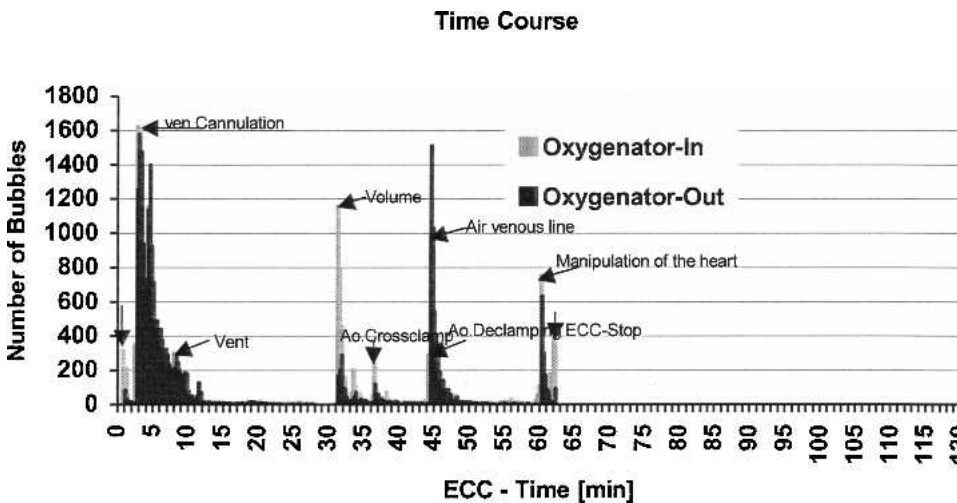


Figure 7. Time course of CABG procedure. Every peak is related with manipulation, which generates bubbles. Bubble activity can be observed in front and behind the oxygenator.

were no significant differences between the oxygenator type statistically. In relation with the different operation procedures, we found more bubbles in the VR group in front of (VR = 7.4 μL/CABG = 5.4 μL) and behind (VR = 3.5 μL/CABG = 2.3 μL) the oxygenator. The reduction rate was comparable (VR = 57.6%/CABG = 53.4%).

Comparing the reduction rate relating to different bubble sizes, we observed quite different behavior for the used oxygenators (Figure 6). In this in vivo cohort, we could confirm the same experiences as Urbanek and Tiedtke observed in their study (11). We discovered that every manipulation during open-heart surgery generates microbubbles (Figure 7). What was remarkable was the

range of reduction rate of the oxygenators shown in Figure 8 and Table 1.

The reduction rate in the in vivo group varied between 0.0% (Affinity) and 50.7% (Hilite) in the range from 10 μm to 45 μm and from 23.6% (Hilite) up to 75.2% (Biocor) in the range >65 μm.

The lower reduction rate of bubbles greater than 45 μm. in the in vivo group comparing with the in vitro group depends on the position of the bubble detection probe, which was placed behind the oxygenator before the arterial filter. Because of the fact that one oxygenator of the in vitro group consisted of a integrated arterial filter (Synthesis), we placed the detector behind the arterial filter unit. Each case often showed a histogram by a greater

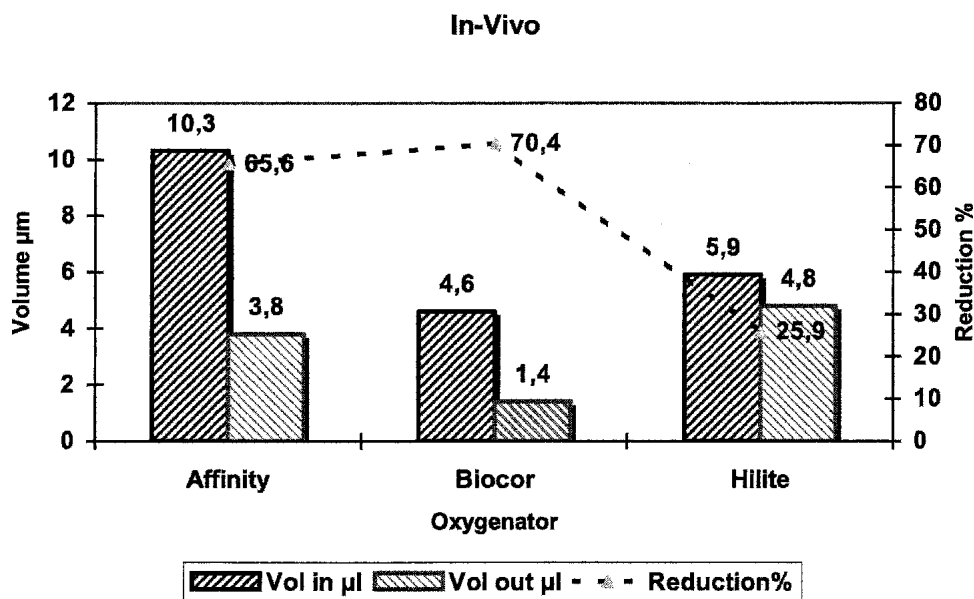


Figure 8. Reduction rate in vivo group of the used oxygenator in total.

Table 1. In vivo group data.

	10–14 µ	15–20 µ	21–30 µ	31–45 µ	45–65 µ	>65 µ	Vol. in µL	Vol. out µL	Reduction%
Affinity (n = 10)	30.7/30.9	14.4/20.5	5.4/12.3	0.5/1.5	3.5/6.1	67.5/9.2	10.3/6.5	3.8/2.9	65.6/8.2
Biocor (n = 9)	16.8/23.9	13.4/19.8	6.3/11.8	0/0	8.2/11.7	76.5/8.8	4.6/5.6	1.4/1.7	70.4/8.1
Hillite (n = 9)	46.4/25.1	49.8/30.7	41.5/27.7	26.4/27.7	15.7/17.9	20.2/22.9	5.9/3.8	4.8/4.0	25.9/20.4
Total (n = 28)	29.6/28.7	24.1/28.3	16.1/24.5	7.7/18.7	8.9/13.2	57.6/28.0	6.8/5.9	3.1/3.2	56.2/23.2
CABG (n = 14)							5.4/3.9	2.3/1.5	53.4/20.5
VR (n = 14)							7.4/6.4	3.5/3.5	57.6/24.7

Results expressed as mean and standard deviation.

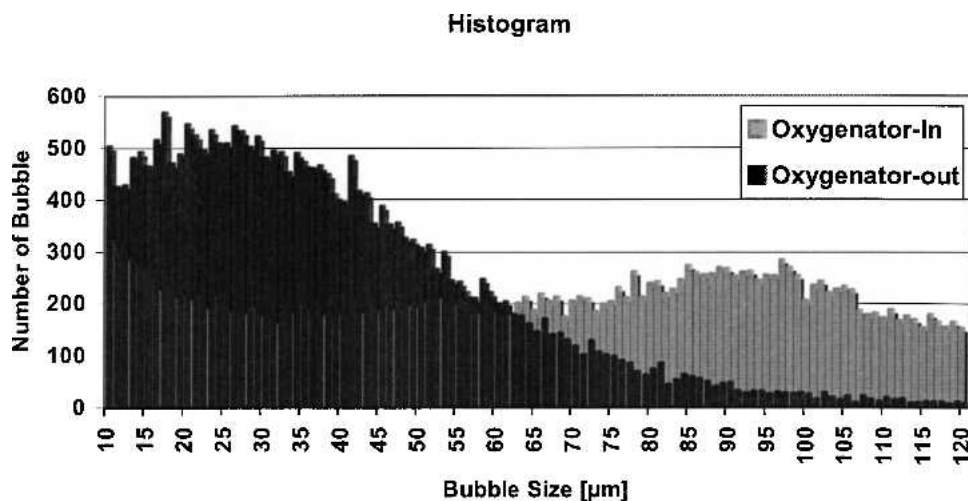


Figure 9. Histogram of bubble activity in front and behind the oxygenator related to their size.

number of small bubbles behind the oxygenator than in front (Figure 9).

In the in vivo group, the Biocor offered the highest reduction rate whereas the Affinity showed the lowest. We assumed that the matt-technology in new oxygenators obviously reduces the number of microbubbles compared with the single-strand technology.

Examining the in vitro cohort, we observed quite different results comparing to the in vivo group (Figures 10 and 11). Overall, in the in vitro trials, we noticed reduction rates from 51.7% to 80% in small bubble sizes and 89.2% up to 97.1% in greater bubble sizes. We can make a precise distinction between the tests (Table 2 and 3). The first three tests, which were performed with Ringer’s solution,

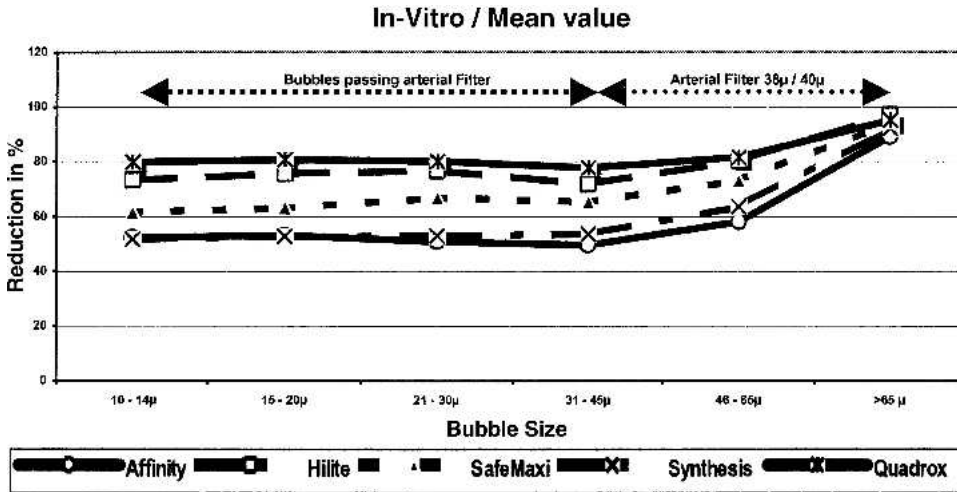


Figure 10. Reduction rate in percent of the in vitro group in relation to bubble size.

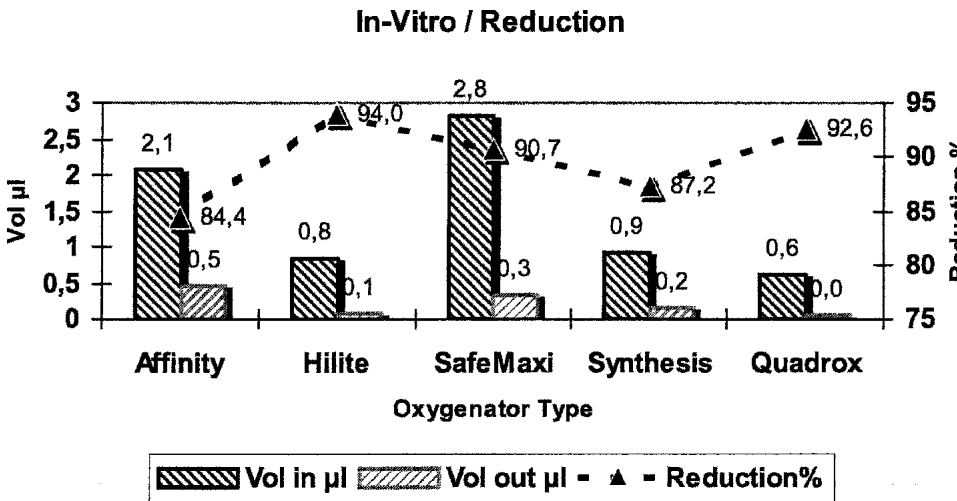


Figure 11. Reduction rate in vitro group of the used oxygenator in total.

Table 2. In vitro test.

Oxygenator	Bubble Size						Vol. in µL	Vol. out µL	Reduction
	10-14	15-20	21-30	31-45	46-65	>65			
1. Test									
Affinity	100	99.9	100	100	99.9	99.9	1.1	0.0008	99.9
Hilite	100	100	100	99.9	99.4	98.9	0.19	0.0004	99.8
SafeMaxi	100.0	100.0	100.0	100.0	99.7	99.4	0.6	0.0	99.9
Synthesis	100.0	100.0	100.0	99.9	99.5	99.2	0.4	0.0	99.9
Quadrox	100	99.6	99.9	100	100	100	0.18	0.0001	99.9
2. Test									
Affinity	81	82	86.5	92.3	97.5	99.3	0.52	0.01	98.1
Hilite	57.6	59.5	64	78.5	91.8	99.3	0.76	0.02	97.4
SafeMaxi	69.3	70.75	75.25	85.4	94.65	99.3	0.64	0.015	97.7
Synthesis	63.5	65.1	69.6	82.0	93.2	99.3	0.7	0.0	97.5
Quadrox	93.7	94.5	96.8	98	99.3	99.4	1.19	0.011	99.9
3. Test									
Affinity	72.9	76.3	80.9	88.5	96.9	99.5	2.17	0.05	97.7
Hilite	98.9	98.9	98.5	99.2	99.4	100	0.188	0.0005	99.7
SafeMaxi	85.9	87.6	89.7	93.9	98.2	99.8	1.2	0.0	97.9
Synthesis	92.4	93.3	94.1	96.5	98.8	99.9	0.7	0.0	98.1
Quadrox	92.9	92.2	96.1	98.9	98.8	97.7	0.46	0.011	97.6

Results of three tests with Ringer's solution are shown.

Table 3. In vitro test.

Oxygenator	10–14	15–20	21–30	31–45	46–65	>65	Vol. in μL	Vol. out μL	Reduction
4. Test									
Affinity	15.1	15.8	7.2	0	0	64.6	3.28	1.36	58.5
Hilite	44.3	56.5	60.5	47.2	67.9	94.1	1.39	0.14	89.9
SafeMaxi	29.7	36.2	33.9	23.6	34.0	79.4	2.3	0.8	67.9
Synthesis	37.0	46.3	47.2	35.4	50.9	86.7	1.9	0.4	76.1
Quadrox	49.1	52.6	50.6	53.8	65.4	93.1	0.744	0.08	89.2
5. Test									
Affinity	28.7	27.2	18.1	9.4	24.3	85.9	2.32	0.57	76.4
Hilite	65.8	67.8	67.4	53.4	63.4	94.8	1.19	0.13	89.1
SafeMaxi	47.3	47.5	42.8	31.4	43.9	90.4	1.8	0.4	80.1
Synthesis	56.6	57.7	55.1	42.4	53.6	92.6	1.5	0.2	83.7
Quadrox	77.4	73.5	68.1	54.3	64.5	91.7	0.163	0.022	86.5
6. Test									
Affinity	16.3	16.9	11.5	6.7	29	86.2	3.1	0.73	76.5
Hilite	72.9	71	70.1	51.9	59.9	95.6	1.37	0.16	88.3
SafeMaxi	44.6	44.0	40.8	29.3	44.5	90.9	2.2	0.4	80.1
Synthesis	58.8	57.5	55.5	40.6	52.2	93.3	1.8	0.3	83.2
Quadrox	66.6	71.5	69.5	60.9	61	88.9	0.91	0.15	83.5

Results of three tests performed with blood are shown.

Table 4. In vitro group.

	10–14 μ	15–20 μ	21–30 μ	31–45 μ	45–65 μ	>65 μ	Vol. in μL	Vol. out μL	Reduction%
Affinity (n = 6)	52.3/36.8	53.0/37.2	50.7/42.7	49.4/48.6	57.9/45.1	89.2/13.8	2.1/1.1	0.5/0.5	84.4/16.8
Hilite (n = 6)	73.3/22.4	75.6/19.2	76.8/17.7	71.7/24.2	80.3/18.5	97.1/2.6	0.8/0.6	0.1/0.1	94.0/5.5
SafeMaxi (n = 6)	61.5/36.9	63.0/34.6	66.8/29.4	65.2/30.9	73.1/26.3	94.1/4.7	2.8/3.9	0.3/0.6	90.7/6.6
Synthesis (n = 6)	51.7/32.7	52.6/30.9	52.9/34.0	53.6/37.5	63.6/34.5	92.1/8.8	0.9/0.7	0.2/0.2	87.2/12.3
Quadrox (n = 6)	80.0/19.5	80.7/17.9	80.2/20.3	77.7/23.5	81.5/19.6	95.1/4.5	0.6/0.4	0.0/0.1	92.6/7.1
Total (n = 30)	61.7/32.2	62.9/30.8	63.8/31.3	62.4/34.0	70.4/30.2	93.4/7.7	1.6/2.3	0.2/0.4	89.6/10.3

Results are expressed as mean and standard deviation.

showed a high reduction between 97.4% and 99.9%. The results of the last three tests performed with blood varying between 58.5% and 89.9% (Table 4).

Comparing the amount of air entering the oxygenator, we observed more air in the in vivo group (total 6.8 μL) compared to the in vitro group (total 1.6 μL). These results were influenced by the length of bypass-time, different surgical procedure, and varieties conducting the bypass.

The higher reduction of bubbles greater 45 μm is affected by the arterial filter with defined pore sizes of 38 μm in the Affinity-filter and 40 μm in the Synthesis oxygenator, but by mean 40% of small bubbles are able passing the arterial filter. It is not clear by which way air traverses the arterial filter—perhaps by distortion or coalescence of fragmented bubbles behind the filter (3).

DISCUSSION

Regarding the current discussion concerning the responsibility of microbubbles in postoperative brain injury, we could demonstrate the different air-handling capabilities of the daily used oxygenators that were brought in to action as well as provoke bubble-generating situations by

in vitro investigation. Using a special bubble-counting device, we were able to detect, quantify, and qualify bubbles smaller than 50 μm .

Previous studies investigated the effective of different extracorporeal circuit elements with different devices and different demand. Beckley et al. proved that not only one factor, such as blood flow orientation, oxygenator design, or the transmembrane pressure, can be isolated as a predictor for air handling capability (12).

There are major differences in present oxygenator technology, concerning the blood flow with varying estimates of reduction. Studying the bubble histograms, we assumed that the oxygenator converted a larger bubbles into many small bubbles, which are able to pass the arterial filter. However, the present cardiopulmonary bypass circuits and their components are not able to eliminate GME completely (13).

Faced by the challenge of minimizing extracorporeal circuits, we have to be aware that minimized circuits don't minimize the risk of GME (14). Everyone who is involved in extracorporeal technology must be aware of the risk of embolization, and research should be done improving circuit components and clinical practice toward eliminating air bubbles.

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