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Original Article

Retrospective Analysis of Air Handling by Contemporary Oxygenators in the Setting of Cardiac Surgery

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Purpose: Cardiac surgery with the use of extracorporeal circulation is associated with a significant risk for gaseous microemboli (GME) despite excellent surgical techniques and highest operative standards. GME are associated with postoperative neurocognitive dysfunction and negative clinical outcome. This study determines whether oxygenator design has influence on perioperative outcome after cardiac surgery.
Methods: Three different oxygenator models with integrated arterial filter (HiliteAF 7000, Fusion Affinity, and Synthesis) were retrospectively evaluated in 55 patients undergoing elective cardiac surgery with the use of extracorporeal circulation. The two-channel ultrasound bubble counter BCC200 was used to detect GME in real time.
Results: All three oxygenators differ in terms of structural specifications and have different rates of number and volume GME reduction. The Fusion Affinity had the lowest arterial GME volume (1.81 μL ± 0.23 μL), which was statistically significant compared to the Synthesis (3.37 μL ± 0.71 μL, p = 0.014). However, the Synthesis had lower absolute numbers at the venous GME count (31771 μL ± 6579 μL) versus the Fusion Affinity (49304 μL ± 8196 μL). However, with regard to clinical outcome after cardiac surgery (duration of invasive and non-invasive mechanical ventilation, incidence of delirium, stroke, acute renal failure, or new myocardial infarction), we found no differences between groups.
Conclusion: Despite significant differences in the design specifications, all oxygenators eliminated relevant GME volumes safely.

Keywords: gaseous microemboli, oxygenator, extracorporeal circulation, perioperative outcome, thoracic surgery

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Introduction

Gaseous microemboli (GME) may occur during several invasive procedures and despite excellent surgical techniques and highest operative standards, the clinical intervention with the highest risk of GME formation is cardiac surgery with the use of extracorporeal circulation.[1,2)] GME are associated with postoperative neurocognitive dysfunction and negative clinical outcome, which have been classified into two subgroups by the "American College of Cardiology," respectively, the American Heart Association guidelines. Group 1 patients suffer from a major focal neurologic deficit, going ahead with stupor or coma, whereas the group 2 dysfunctions

include confusion, memory deficits, seizures, etc.[3,4] Overall, the clinical outcome after suffering from GME during cardiac surgery is determined by size and location of the GME, as well as by general status and comorbidities of patients. Massive GME are usually fatal, both in the venous and arterial circulation.[5] If large gaseous embolisms migrate into the pulmonary circulation and obstruct the right ventricular outflow, this pulmonary embolism increases resistance in the right ventricle and leads to reduction of left ventricular preload.[1] Although GME could concern any organ, occlusion of cerebral and cardiac circulation are especially harmful as these systems are highly vulnerable to ischemia.[3] In addition, GME interact with blood cells (leucocytes and platelets) and initiate an inflammatory response. The inflammatory cascade then itself causes an exacerbation of the cerebral injury.[6] Studies showed that the greater the number of GME, the worse the cognitive outcome for patients after cardiac surgery.[7] Similar applies to the rate of perfusionists' interventions: an increased number of interventions during extracorporeal circulation leads to an increased number of GME, which has a negative impact on the postoperative course after cardiac surgery.[7] Despite the fact that recent membrane oxygenators can eliminate large amounts of potential GME from the extracorporeal circuit via the venous reservoir, the oxygenator- and the arterial line filter,[8] still 30% of patients even experience long-term complications.[6]

Previous studies showed that regarding GME-prevention common oxygenators have significantly different capacities to reduce the amount and volume of GMEs.[6,9,10] However, until now, no study investigated whether the type of oxygenator has impact on clinical outcome after cardiac surgery. We therefore performed a respective analysis with the hypothesis that the type of oxygenator affects the clinical outcome after cardiac surgery with extracorporeal circulation. The aim of our study was to test this hypothesis by comparing three common oxygenator designs retrospectively with special focus on perioperative outcome after cardiac surgery.

Materials and Methods

Study design and patients

We performed a retrospective analysis of patients that underwent cardiac surgery between May and June 2016 at the University Hospital of the RWTH Aachen (Germany). In all, 55 patients undergoing elective cardiac surgery with the use extracorporeal circulation were consecutively assigned to be perfused with three different oxygenator models with integrated arterial filter: the HiliteAF 7000 (Medos Medizintechnik AG, Stolberg Rhineland, Germany), the Fusion Affinity (Medtronic Minneapolis, MN, USA), or the Synthesis (Sorin Group/LivaNova, Mirandola, Italy). All three oxygenators are comparable with regard to their cylindrical hollow fiber bundles, the same fiber material, and similar maximum volume flows; however, differences in the design specifications of the three models are presented in **Table 1**. We excluded patients with preoperative neurologic incidents, emergency, or re-do procedures.

Operative management

Patients received perioperative care according to institutional standards. Standard cardiovascular and respiratory monitoring such as heart rate, peripheral oxygen saturation, and non-invasive and invasive arterial blood pressure were continuously monitored.

Surgical management consisted of a full median sternotomy and therapeutic heparinization to an activated clotting time (ACT) >400 sec, followed by the establishment of extracorporeal circulation with arterial inflow through the ascending aorta and venous drainage through a single two-stage right atrium cannula. Myocardial protection consisted of mild to moderate hypothermia (32–28°C) and cold antegrade crystalloid cardioplegic solution (CustodiolTM, Koehler Chemie, Alsbach-Haehnlein, Germany).

Extracorporeal circulation

All included patients underwent cardiac surgery with a conventional cardiopulmonary bypass (CPB) circuit (Stockert s5, Sorin Group Germany, Munich, Germany). After cross-clamping, cardiac arrest was induced by antegrade infusion of cold crystalloid cardioplegic solution (CustodiolTM, KoehlerChemie). Extracorporeal circulation was performed with a non-pulsatile pump flow of 2.2 L min^{-1} m^{-2}.

Gaseous emboli counter

GME were measured in real time using a two-channel ultrasound bubble counter BCC200 (GAMPT, Merseburg, Germany). GME ranging from 10 to 500 μm were counted and classified as "over range" higher than 500 μm. GME were detected and measured cumulatively during the overall extracorporeal circulation time.

Postoperative clinical evaluation

Postoperative clinical endpoints included duration of invasive mechanical ventilation on intensive care unit (ICU)

Table 1 Specifications of study oxygenators and patient characteristics

	Medos Hilite (n = 19)	Medtronic (n = 18)	Sorin Synthesis (n = 18)
Specifications of oxygenators			
Blood flow rate (max)	7 L/min	7 L/min	8 L/min
Filling volume	320 mL	260 mL	430 mL
Gas exchanger material	Polypropylene	Polypropylene	Polypropylene
Gas exchanger surface	1.9 m²	2.5 m²	2 m²
Heat exchanger material	Polyethylene	Polyethylene terephthalate (PET)	Stainless steel
Heat exchanger surface	0.45 m²	0.4 m²	0.14 m²
Pore size arterial filter	40 µm	25 µm	40 µm
System coating	x.eed coating	Balance Biosurface	Phosphorylcholine coating
Pressure loss at max. blood flow	Approx. 190 mmHg	Approx. 160 mmHg	Approx. 260 mmHg
Heat exchanger performance factor at max. blood flow	Approx. 55%	Approx. 50%	Approx. 35%
Flow guidance	Substantially longitudinally directed, initially along the heat exchanger fibers, then longitudinally along the gas exchange fibers	First through the heat exchanger, which is installed below the gas exchanger. In the fiber bundle (separate housing) cross-flow	First along the heat exchange fibers. Then “wavy” through the fiber bundle. Filter separately in a chamber placed around the gas exchange bundle
Patient characteristics			
Age	63.74 ± 7.25	66.28 ± 9.5	68.89 ± 8.18
Sex (male/female)	19/0	12/6	13/5
Pre-existing conditions			
Diabetes mellitus Type 2	7	2	6
Arterial hypertension	14	13	12
Anti-coagulation therapy			
Aspirin	15	15	8
Marcumar	1	2	4
Other	5	0	0
Adiposities per magna (BMI >30)	8	8	4
Current tobacco use	10	10	5
Cardiac surgery			
CABG surgery	15	13	13
Valve surgery	4	5	5
CPB time (min)	118.32 ± 37.70	113.17 ± 28.72	126.50 ± 61.28
Aortic cross-clamp time (min)	74.63 ± 28.22	70.56 ± 20	73.28 ± 29.72
Reperfusion time (min)	31.89 ± 10.43	36.31 ± 11.20	38.61 ± 8.18
Minimal blood temperature (°C)	30.21 ± 2.31	29.88 ± 1.93	29.61 ± 2.65

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; BMI: body mass index

in hours, duration of non-invasive mechanical ventilation on ICU in hours, diagnoses of delirium during hospital stay, as assessed by the confusion assessment method for the ICU (CAM-ICU). Furthermore, diagnosis of stroke during hospital stay (defined as any new, temporary or permanent, focal or global neurologic deficit evaluated according to the National Institutes of Health Stroke Scale, with stroke defined as a score of ≥4 points on a scale of 0 to 42, with higher scores indicating greater severity). Acute renal failure during hospital stay was defined as followed: Increased serum creatinine level: ≥0.3 mg/dL compared to Baseline (BL) within 48 hours, or increased serum creatinine level by a factor of ≥1.5 compared to BL within 7 days, or decreased urine output of ≤0.5 mL kg^{-1} h^{-1} for minimum 6 hours. Myocardial infarction during hospital stay was referred to as increase in biomarkers (e.g., troponin), values more than five times the 99th percentile of the normal reference range plus one or more of the following: new pathologic Q waves or new left bundle-branch block within the first 72 hours after surgery, standard clinical criteria for myocardial infarction from 72 hours onward, a new finding of ischemia by echocardiography or angiography.

Statistical analysis

All data were statistically analyzed using a commercially available software package (GraphPad Prism 6.0, Graphpad Software Inc., San Diego, CA, USA). All data were tested for normal distribution with the Shapiro–Wilk's test. Normally distributed data were compared using one-way analysis of variance (ANOVA and for the adverse events in outcome (delirium, stroke, myocardial infarction, acute renal injury) using a two-way repeated-measures ANOVA). If the group effect was significant, a Tukey post-hoc test was used for pairwise comparisons between all groups. In case of non-normal distribution, a Kruskal–Wallis test followed by a Dunn's post-hoc test was used. In all cases, a level of $p < 0.05$ was considered as statistically significant.

Results

Patient characteristics

Demographic and surgical data did not differ significantly between the three groups; details are presented in **Table 1**. Additionally, the average amount of heparin per kg bodyweight during surgery was equal for all the groups, without significant differences (Medos Hilite n = 19: 438 ± 111 IU/kg, Medtronic n = 18: 479 ± 120 IU/kg, Sorin Synthesis n = 18: 495 ± 167 IU/kg). No mortality was observed in the Medos Hilite, and the Sorin Synthesis group, one patient from the Medtronic fusion group died during the postoperative course on ICU; all other patients were discharged from hospital without neurologic complications.

Number and volume of GME reduction

In **Fig. 1** and **Table 2**, the number and volume reduction rates of the three oxygenators are presented. All three oxygenators had different rates in number and volume GME reduction. The Fusion Affinity had the lowest arterial GME volume (1.81 µL ± 0.23 µL), which was statistically significant compared to the Synthesis (3.37 µL ± 0.71 µL, p = 0.014). However, the Synthesis had lower absolute numbers at the venous GME count (31771 µL ± 6579 µL) versus the Fusion Affinity (49304 µL ± 8196 µL). No significant differences were shown between the HiliteAF 7000 and the Fusion Affinity or the HiliteAF 7000 and the Synthesis.

Perioperative outcome after cardiac surgery

In all three groups, we observed the usual rate of postoperative complications after cardiac surgery. With regard to invasive and non-invasive mechanical ventilation, we found no statistically significant difference between all three groups. The incidence of delirium, stroke, acute renal failure, or new myocardial infarction did not differ between the three groups (**Table 2** and **Fig. 2**). Regarding the severity of stroke, in only one out of five stroke events reported in this study, the manifestation of neurocognitive disorders was documented. The four other cases remained without impairment of the neuronal function. Thus, in total for one patient out of 55, we could prove severe stroke-related disorders.

As shown in **Table 3**, only one of the five postoperative stroke patients had a history of cerebrovascular disorder prior to the surgery, and the same patient showed a carotid stenosis at the preoperative tests. Furthermore, in only one of the stroke patients preoperative and postoperative atrial fibrillation was reported, whereas in total three out of five stroke patients showed only postoperative atrial fibrillation.

Discussion

In this study, the impact of the oxygenator-type on clinical outcome after cardiac surgery was investigated and the air-handling capacity of three oxygenators is

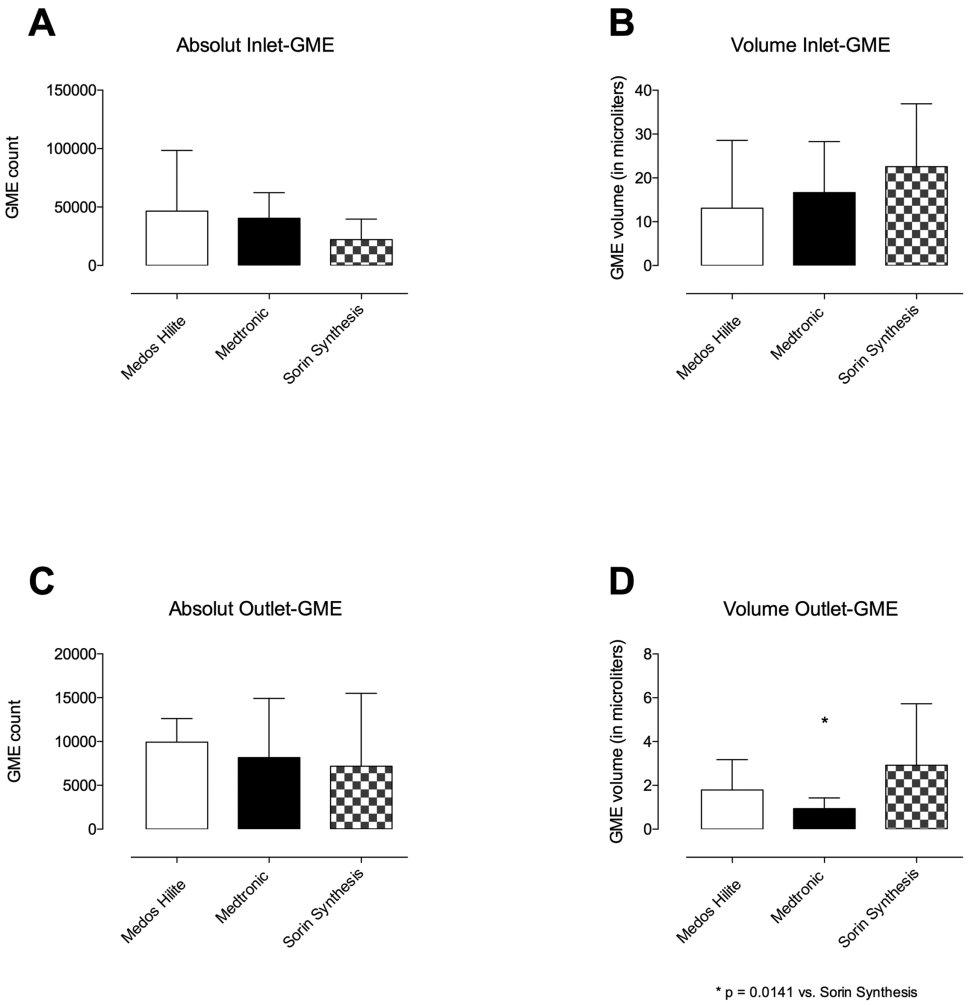

Fig. 1 Absolute counts (Panel **A**) and volumes (Panel **B**) of GMEs detected in inlet line and absolute counts (Panel **C**) and volumes (Panel **D**) of outlet line of the used oxygenators. White bar: Interventional group treated with the Medos HiliteAF oxygenator. Black bar: Interventional group treated with the Medtronic oxygenator; Squared bar: Interventional group treated with the Sorin Synthesis oxygenator; Values are displayed as means ± SD. All data presented as total GME counted during the operative procedure. GME: gaseous microemboli; SD: standard deviation

Table 2 Volume and number of GME entering (arterial) and leaving (venous) the oxygenator + clinical outcome after cardiac surgery

	Medos Hilite (n = 19)	Medtronic (n = 18)	Sorin Synthesis (n = 18)	p value
Venous GME volume (µL)	17.84 ± 14.28	18.82 ± 13.27	25.08 ± 17.26	0.3345
Arterial GME volume (µL)	2.39 ± 0.48	1.81 ± 0.23*	3.37 ± 0.71	*0.014 Fusion vs. Synthesis
Venous GME count	56841 ± 9466	49304 ± 8196	31771 ± 6579	0.122
Arterial GME count	9753 ± 5042	10512 ± 1366	9744 ± 1869	0.9173
Duration invasive mechanical ventilation (hours)	65.74 ± 148.95	115.79 ± 247.80	59.09 ± 133.86	0.5990
Duration non-invasive mechanical ventilation (hours)	2.75 ± 4.43	3.5 ± 4.79	2.75 ± 5.34	0.8661
Delirium	3	5	2	0.633
Stroke	2	1	2	1.0
Acute renal failure	4	7	3	0.525
New myocardial infarction	1	0	0	1.0

Data are reported as mean ± standard deviation (SD). GME: gaseous microemboli

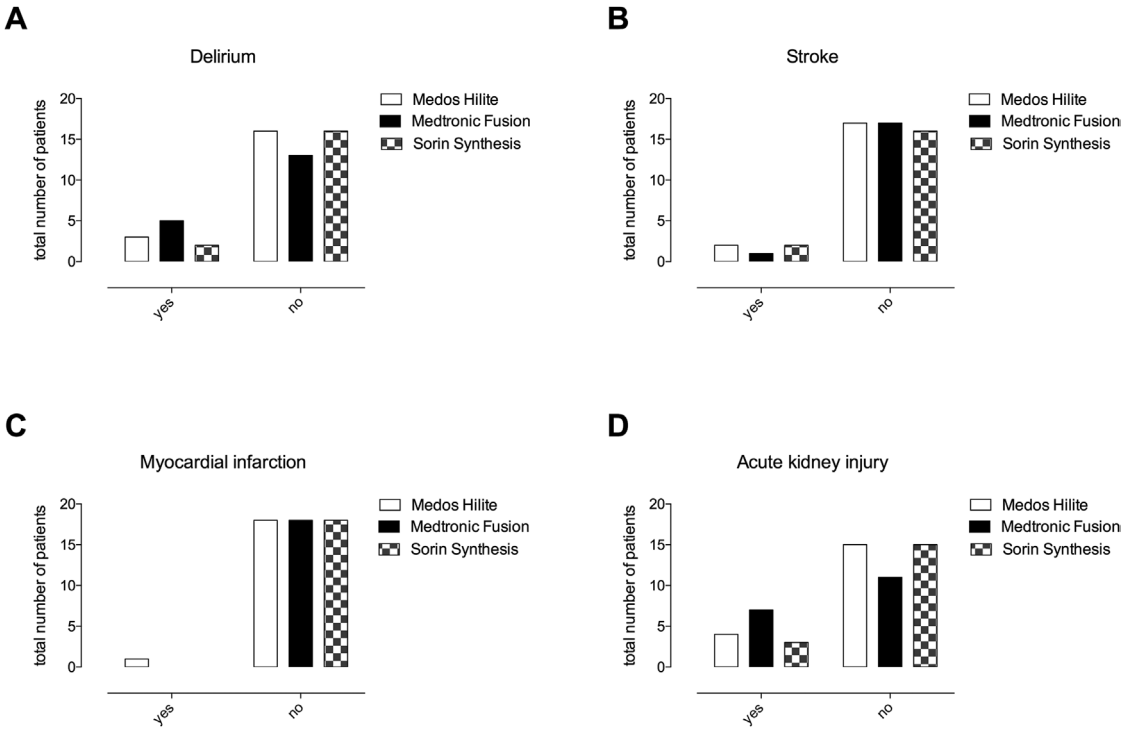

Fig. 2 Comparison of absolute counts of adverse events between the used oxygenators. (Panel **A**: Delirium; Panel **B**: Stroke; Panel **C**: Myocardial infarction; Panel **D**: Acute kidney injury). White bar: Interventional group treated with the Medos HiliteAF oxygenator. Black bar: Interventional group treated with the Medtronic oxygenator; Squared bar: Interventional group treated with the Sorin Synthesis oxygenator; Values are displayed as means ± SD. All data presented as total number of adverse events counted during the postoperative course on ICU. ICU: intensive care unit; SD: standard deviation

Table 3 Preoperative and postoperative diagnosis of potential risk factors for stroke after cardiac surgery

Stroke patient (no.)	"Preoperative atrial fibrillation" (1 = yes/0 = no)	"Postoperative atrial fibrillation" (1 = yes/0 = no)	"History of cerebrovascular disorder prior to surgery" (1 = yes/0 = no)	"Carotid stenosis at the preoperative test" (1 = yes/0 = no)
1	0	1	0	0
2	1	1	0	0
3	0	0	0	0
4	0	1	0	0
5	0	0	1	1
Sum out of five	1	3	1	1

described. The results show that although all three oxygenators differ in terms of structural specifications and have different rates of number and volume GME reduction, only the Fusion Affinity compared to the Synthesis had a statistically significant lower arterial GME volume. However, with regard to clinical outcome after cardiac surgery (duration of invasive and non-invasive mechanical ventilation, incidence of delirium, stroke, acute renal failure, or new myocardial infarction), we found no differences between the three groups. From these results, it is safe to conclude that recent oxygenators feature bubble traps and arterial filters, which certainly remove bubbles of critical size (>500 μm) and volume (>120 μL),[11] as the volumes of detected GME ranged from 17.8 to 25.1 μL in the venous circuit and from 1.8 to 3.3 μL in the arterial circuit.

These results are underlined by data from experimental animal studies, which showed that even 120 μL of air reaching the middle cerebral arteries (MCA) do not cause cerebral injury.[12] Interestingly, clinical trials support our findings, using transcranial Doppler technology (TCD) in 10 patients.[11] Chung and colleagues found that

although if the amount of bubbles, respectively, microembolic events in the arterial system during surgery is excessively high (>18 k), the majority of the bubbles is too small to be harmful.[11] In comparison, the amount of microembolic events in our study was ~9 k. Thus, clinical outcome, with regard to delirium, stroke, acute renal failure, and new myocardial infarction during the perioperative course, is not related to the GME formation during cardiac surgery with extracorporeal circulation. Nevertheless, in comparison to the reported incidence of stroke during CPB surgery of 1.3–3.6%,[13] the occurrence of stroke in our study was 9%, independent from the group. Especially for patients undergoing coronary artery bypass grafting, the incidence for stroke is reported up to 5%,[14] often related to a history of stroke for the patients, or arthrosclerosis.[15]

Other experimental studies focused exclusively on air-handling properties of current oxygenators. Qiu et al.[12] evaluated the Capiox FX05, Wang et al.[16] tested Capiox RX25 and the Quadrox-I, both concluded that in a simulated adult CPB circuit the oxygenators performed well. Their findings are in line with the results from a Swedish team,[17] who also conclude that incorporated arterial filters reduce GME activity. Our study emphasizes the findings from these experimental studies to clinical results.

It is safe to conclude from our study that all three investigated oxygenators performed well in the setting of cardiac surgery although differences in design and filtration specifications are present. Both the Synthesis and Hilite oxygenator are axial flow devices with high resistances, which deliver higher pressure differentials independently form the flow applied. The Fusion oxygenator has a radial flow membrane with low pressure differentials which are therefore flow-dependent. Only the Hilite and the Synthesis oxygenator have polyester-based filter systems, whereas the Fusion does not provide a polyester-integrated filter.

Our findings of the lowest arterial GME volume found in the Fusion Affinity can be interpreted in the context of its membrane bundle configuration that creates greater resistance to increasing flows than the other oxygenators that use radial flow membrane bundles. This membrane configuration seems to filter GME more efficiently through its polypropylene hollow fibers.

Pressure loss at maximum blood flow varies from 160 mmHg (Fusion Affinity) to 260 mmHg (Synthesis). The gas exchanger surface of the Fusion Affinity (2.5 m²) is approximately 25% larger than the gas exchanger surface of the HiliteAF 7000 or the Synthesis. A large surface is often interpreted as an indication of high blood damage (especially platelet activation).[18,19] In addition, a large surface indicates inefficient mass transfer.[19] This has particular effects on the handling (priming behavior before use, or venting behavior, if air entered the oxygenator during use). Nevertheless, those differences in design specifications had no causal relationship with clinical outcome after cardiac surgery.

Limitations

Our study has several limitations; the major limitation is the retrospective nature of our study. Our findings should therefore be confirmed in future prospective randomized trials. It also suffers from the small cohort size and following studies could emphasize our results in larger populations. While this study has demonstrated a number of differences between the three evaluated oxygenators, it cannot be extrapolated to all conventional oxygenator types.

Conclusion

We conclude that all three investigated oxygenators effectively eliminated any clinically relevant amount of GME in the setting of cardiac surgery. Despite significant differences in the design specifications, the tested oxygenators also eliminated any relevant GME volumes safely. Thus, no impact of these oxygenators on the clinical outcome after cardiac surgery was detected.

Disclosure Statement

All authors state that they have no conflict of interest.

The company enmodes GmbH provides design and engineering services to medical device companies with a major focus on validated computational analyses and optimizations.

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