DELIVERY OF VAPORS ON CARDIOPULMONARY BYPASS USING DIFFERENT OXYGENATOR MEMBRANES

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ABSTRACT

Objectives: World wide about 1,000,000 patients undergo cardiopulmonary bypass (CPB) related procedures every year. Anaesthetic vapors, such as Sevoflurane and Isoflurane, have shown neuro- and cardio-protective effects and are used widely during CPB. Modern oxygenators are using different types of hollow-fibers and the question arises, if vapor molecules effectively travel through these membranes to be delivered to the patient blood during CPB.

Methods: An artificial CPB circuit study (human blood, hematocrit 30, 30°C) is presented. An oxygen-mixture with 2% vapor at 1l/min is delivered to the oxygenator. The vapor concentration in the reservoir is recorded over time until a stable concentration is obtained, then the gas stream is switched to vapor free room air.

Results: The Quadrox D, Maquet (dense polymethylpentene membrane) as compared to the Synthesis, Sorin (micro-porous polypropylene membrane) shows relative limited performance in delivery of vapors (Sevoflurane < Isoflurane).

Conclusions: An artificial CPB circuit is used to test physico-chemical properties of different membranes. The oxygenator model using a plasma-tight (as compared to porous) membrane shows relative limited performance in delivery of vapors through the membrane, suggesting a limited use of plasma-tight membranes for clinically relevant and cost-effective delivery of vapors during CPB to achieve neuro- and cardio-protection.

KEY WORDS
Reliability and Failure, Oxygenator, Cardiopulmonary Bypass (CPB), Sevoflurane, Isoflurane

1. Introduction

One of the basic problems with the use of Cardiopulmonary Bypass (CPB) in cardiac surgery is the delivery of anaesthetic drugs to the patient.

Maintenance of anaesthesia during CPB can be achieved by two basic principles: Delivering anaesthetic drugs solely intravenously (TIVA, Total Intravenous Anaesthesia) or by administering a volatile anaesthetic agent via the membrane oxygenator.

The second principle, however, supposes that the administered volatile anaesthetic can penetrate the various types of membranes of the different membrane oxygenators used in clinical practice.

Dense (PMP, poly-4-methyl-1-penten) membrane oxygenators were introduced to overcome the well known problems regularly appearing when using conventional micro porous (PPL, polypropylene) membrane oxygenators such as the generation of micro bubbles, blood trauma or plasma leakage during long-term application of CPB.

Considering that glassy polymers used in dense PMP membranes usually show a preferred permeability to smaller molecules this effect may be caused by a very low perfusion coefficient of the volatile agent in the solid layer of the dense membrane due to its molecular size.

Own studies using the nobel gas Xenon as an anaesthetic and organ protective showed that this gas is traveling easily through different membranes of oxygenators [1].

Coronary artery bypass grafting (CABG) and valve repair have become standard methods in cardiac surgery. World wide about 1,000,000 patients undergo cardiopulmonary bypass (CPB) related procedures every year [2]. With the improvement in surgical technique and anaesthesia, CABG is now being offered to patients with more severe underlying disease and co-morbidities that may further increase the risk of its complications. The complications following CABG include minor and major postoperative neuro-cognitive decline and other organ dysfunction.
Cognitive studies carried out within days or weeks after surgery have revealed a wide range of short-term cognitive decline [3,4]. Although the past 50 years have brought improvements in extracorporeal technology, including improved gas exchange devices, venous reservoir construction, and heparin-coated circuits, the modern CPB is still remarkably similar to that developed a half century ago. However, over the last decade, a large body of research has substantially improved our understanding of the pathophysiology induced by CPB. Although we have learned much, the substantial morbidity still suffered by patients managed with CPB, amply demonstrates that we have more to learn than we have mastered. Adverse outcomes associated with bypass (Type I central nervous system events, 3%-6%; long-term cognitive dysfunction, 15%; renal dysfunction, 7%-9%; hemodialysis, 1%-2%) are substantial. [5]

In the variety of clinical indications, the need for neuro protection is described best for cardiac patients. Ischemic cerebral complications represent the leading cause of morbidity after cardiac operations. The reported incidence of peri-operative stroke as a major neurologic complication varies from 0.4 to 5.4%, and in-hospital neuropsychological dysfunction as a minor neurologic problem occurs in 25-79% of the cases [6]. The underlying pathology consists of a variety of mechanisms, e.g., hemodynamic fluctuations, cerebral embolization of atherosclerotic plaque, air, fat and platelet aggregates caused by CPB and surgical procedure. These mechanisms induce an imbalanced state of oxygen supply and demand causing major (type I, fatal cerebral injury and nonfatal strokes) and minor (type II, new deterioration in intellectual function or new onset of seizures) neurologic complications [6,7,8,9] One of every $10 spent on surgical treatment of coronary disease is related to a complication in the United States. As compared with patients without adverse neurologic outcome, type I neurologic complications are responsible for an additional $10,266 per patient in in-hospital boarding costs, and type II events are responsible for an additional $6,150 per patient. When one applies these estimates to the 800,000 patients per year who undergo coronary surgery throughout the world, the additional in-hospital cost is approximately $400 million annually. The expense of long-term out-of-hospital medical and rehabilitative services probably results in additional expenditure of some $2 billion to $4 billion annually [6]. With the growing awareness of their social and economic importance, increasing attention is being given to neuroprotective strategies, not only in cardiac anaesthesia. Recently anaesthetic vapors such as Sevoflurane and Isoflurane have shown neuro and cardio protective effects and are used widely during CPB [10]. These vapors also do not show the well-known disadvantages of Xenon such as high price and, low availability and other limitations.

As the transfer characteristics of volatile anaesthetic agents through different membranes are to date not fully understood, several studies are published to elucidate the physico-chemical properties of micro porous and dense membranes.

Schienagel et al. performed a prospective randomized study comprising 75 patients to study the transfer rate of Isoflurane in five different types of membrane oxygenators. An extraction of volatile anaesthetic agent could be clearly demonstrated for micro-porous capillary membrane oxygenators. Administering a defined inspiratory concentration of 1.0% Isoflurane into the gas inlet port of these types of oxygenators yielded significantly lower expiratory concentrations measured at the gas outlet port, after an equilibration period of 10 minutes. The expiratory Isoflurane concentrations, measured in the dense membrane type oxygenators (QUADROXo und Hilite 7000 LT), was, however, only negligibly lower than the inspiratory concentrations. Consequently, Schienagel postulated that there is no adequate transfer of the volatile anaesthetic agent across the new type of diffusion membrane [11].

Prasser et al. have demonstrated that volatile anaesthetics have cardioprotective properties during open-heart procedures, especially when administered continuously. Since the uptake of volatile anaesthetics via diffusion membrane oxygenators is severely reduced, Prasser et al. hypothesized that clinically relevant concentrations of Sevoflurane will remain in the patients' blood following saturation with a volatile agent before start of CPB.

This study was designed to compare conventional and diffusion membrane oxygenators regarding their in vivo elimination of Sevoflurane. Twenty patients undergoing elective coronary bypass surgery were randomly allocated to two groups, either using a micro porous membrane oxygenator or a dense membrane oxygenator in a miniaturized extracorporeal circuit. Anaesthesia was maintained with Sevoflurane, which was stopped at the start of CPB. During CPB, the Sevoflurane concentration was measured in blood and in the exhausted gas from the oxygenator. The elimination of Sevoflurane, expressed as the relative blood concentration, was significantly increased in micro porous membrane oxygenators as compared to dense membrane oxygenators. This resulted in an approximately threefold higher Sevoflurane blood concentration in the dense membrane group over the course of CPB. With the incorporation of dense membrane oxygenator in a miniaturized bypass circuit, relevant concentrations of a previously applied volatile agent could be maintained even without further supply throughout CPB. Prasser et al. concluded that this might be an alternative approach to cardio-protection when Sevoflurane cannot be administered through CPB [12].

Modern oxygenators are using different types of hollow fiber membranes that are specifically designed for the exchange of CO2 and O2 and the question arises, if those different membranes allow larger molecules like...
Sevoflurane and Isoflurane to effectively travel through the membrane to be delivered to the patient blood during CPB.

The present study was designed to compare in vitro the membrane performance of two different oxygenators regarding differences of the transfer over the membrane for Sevoflurane or Isoflurane in an realistic artificial circuit to overcome the limitations of former in vivo studies performed in different patients using different treatment regimes.

The question arises whether there are differences in performance between the two different membrane oxygenator types carrying either a conventional micro porous hollow fiber membrane or the dense hollow fiber membrane.

2. Material and Methods

An artificial CPB circuit is designed consisting of a venous reservoir, oxygenator, roller pump, water bath, Sevoflurane Vaporizer, Isoflurane vaporizer and two patient monitors.

The venous reservoir (Sorin Synthesis, Germany) is modified by removing the filter unit and resealing it airtight. All unused ports are sealed tight. The reservoir is connected to a gas circulating fan unit to avoid layering of the heavy vapors in the air space. Two patient monitors (Datex Engstrom, Finland) are used for continuous measurement of the different pressures, blood temperature and for gas sampling in the reservoir and the gas feed. The sampling gas stream from the reservoir is recirculated to the reservoir to not influence the closed volume. Both patient monitors are calibrated after a warm-up time of 15 minutes prior to the experiment.

The reservoir is filled with 1.3 liters of human blood adjusted to a hematocrit of 30 using Normosol-R (PH 7.4, Hospira, Canada) that is normally used for priming the Cardiopulmonary Bypass.

The blood is circulated from the reservoir outlet by a roller pump (Stöckert Shiley, Germany) at 2l/min into the venous inlet of the oxygenator and from the arterial outlet back into the reservoir using the venous inlet. The blood pressure pre and post the oxygenator are monitored.

The temperature exchange unit of the oxygenator is connected to a refrigerated and heated circulating water bath (Polyscience, USA) that allows the temperature of the blood to be adjusted to (30±0.3)°C.

The gas input of the oxygenator is connected to 2 gas sources controlled by a flow meter (Scott Specialty Gases, Canada) carrying either pressurized room air or premixed 5% CO2 in Oxygen (Praxair, Canada). Sevoflurane (Abbott, Canada) and Isoflurane (Baxter, Canada) can be added to the gas stream by a Sevoflurane or Isoflurane vaporizer (Draeger, Germany).

The gas input pressure and composition as well as the output gas composition is monitored by a patient monitor. At the start of the experiment the blood is circulated at 2l/min while de-nitrogenating the reservoir and the oxygenator by flushing both with 5% CO2 in Oxygen at 6l/min until a stable gas concentration and temperature is reached in the whole system.

The gas delivery to the reservoir is then stopped and the reservoir is closed. The flow to the oxygenator is adjusted to 1l/min of 5% CO2 in Oxygen and Sevoflurane or Isoflurane respectively are added with 2,0% (t = 0 hours).

The Sevoflurane reservoir concentration is recorded over time along with the exhaust concentration over time. After a stable concentration in the reservoir is reached, the gas stream is switched to vapor free room air at 1l/min (t = 2 hours for Sevoflurane and t=2h 22min for Isoflurane).

![Figure 1: Schematic setup of the artificial CPB circuit for Sevoflurane (Isoflurane is identical)](image-url)
3. Results

The Quadrox D oxygenator, containing a dense, as compared to the Synthesis oxygenator, containing a porous membrane, shows very limited performance in delivery of vapors through the membrane whereas the Isoflurane performance is superior to the Sevoflurane performance.

3.1 Results for Sevoflurane

After de-nitrogenating the system, the Sevoflurane concentration of 2% was achieved and the delivering gas mixture measured 5% CO₂ in Oxygen. The gas flow was measured at 1l/min.

From 0 to 2 hours (wash in phase) the concentration of Sevoflurane in the blood is measured by means of headspace gas measurement in the reservoir and recorded over time:

Using the Synthesis oxygenator, the Sevoflurane concentration in the blood eventually reached a steady state at 1.5% after 1h 30min.

Using the Quadrox D oxygenator, the Sevoflurane concentration in the blood slowly increased up to 0.25% not reaching a steady state. Within a realistic time frame of two hours it was not possible to reach a clinically relevant concentration of Sevoflurane in the blood.

After 2 hours the gas stream is switched to room air at 1l/min (wash out phase), which was proven to not be contaminated by Sevoflurane:

Using the Synthesis oxygenator, the Sevoflurane concentration in the reservoir reached the lower threshold of the analyzer (0.1%) after 1h 30min.

As there was no clinically relevant concentration of Sevoflurane in blood could be reached with the Quadrox D oxygenator, no wash out phase was recorded.

Figure 2: Sevoflurane concentration in blood (%) for Sorin Synthesis (red/orange) and Quadrox D (black/grey) over time during wash in and wash out procedure as a function of transport of vapor through the different membranes.

3.2 Results for Isoflurane

After de-nitrogenating the system, the Isoflurane concentration of 2% was achieved and the delivering gas mixture measured 5% CO₂ in Oxygen. The gas flow was measured at 1l/min.

From 0 to 2 hours (wash in phase Sorin oxygenator) and from 0 to 2h 20min (was in phase Quadrox D oxygenator) the concentration of Isoflurane in the blood is measured by means of headspace gas measurement in the reservoir and recorded over time:

Using the Synthesis oxygenator, the Isoflurane concentration in the blood eventually reached a steady state at 1.5% after 1h 30min.

Using the Quadrox D oxygenator, the Isoflurane concentration in the blood eventually reached 0.96%, reaching a steady state after 2h 20min.

After 2 hours the gas stream is switched to room air at 1l/min (wash out phase), which was proven to not be contaminated by Isoflurane:

Using the Synthesis oxygenator, the Isoflurane concentration in the reservoir reached the lower threshold of the analyzer (0.1%) after 1h 30min.

Using the Quadrox D oxygenator, the Isoflurane concentration in the reservoir reached the lower threshold of the analyzer (0.1%) after 2h 40min.

As the Quadrox D oxygenator #I broke after the Sevoflurane experiment, only data for Quadrox D oxygenator #II were recorded.

Figure 3: Isoflurane concentration in blood (%) for Sorin Synthesis (red/orange) and Quadrox D (black) over time during was h in and wash out procedure as a function of transport of vapor through the different membranes.
4. Conclusion

Our study demonstrates a markedly different performance of oxygenators using either a conventional micro porous hollow fiber membrane or the dense hollow fiber membrane in an artificial CPB setting. Thus, the hypothesis, that different membranes with different physico-chemical properties are resulting in a different performance for delivering Sevoflurane or Isoflurane on the CPB are confirmed. Diffusion membrane oxygenators have primarily been developed to eliminate the well known problems, that regularly appear when using conventional micro porous hollow fiber membrane oxygenators, e.g. the generation of micro bubbles, blood trauma during CPB or plasma leakage during long term application. The wall structure of the dense hollow fiber membrane consists out of a highly porous support matrix and a thin (0.05 µm) tight membrane on the blood side of the matrix, which constitutes a solid barrier between the blood and the gas phase. The homogeneous tight membrane and the complete separation of blood and gas phases obviously provide a better biocompatibility with less blood trauma. Crossing of micro bubbles as well as plasma leakage does not occur due to tightness of the membrane.

Unfortunately, the uptake of Sevoflurane and Isoflurane into blood via dense membrane oxygenators during CPB is severely limited in patients as recently demonstrated by Wiesenack [13] and Prasser et al. [12].

These results published by Prasser, who investigated the washout phase and elimination of Sevoflurane during minimal CPB, are supporting our observations. Prasser could show a relative decrease in the Sevoflurane blood concentrations after start of CPB with micro porous and dense membranes. Furthermore he described the Sevoflurane concentration in the oxygenator gas exhaust, where there was no measurable washout of Sevoflurane in the dense membrane group as compared to wash out concentration of the micro porous membrane group. As Prasser could only show wash out concentrations and only for Sevoflurane we could reconfirm these results. But furthermore we show performance data for the wash in and wash out phase for Sevoflurane and Isoflurane.

In an other study by Schienagel et al. the exhaust gas concentrations of Isoflurane, measured in the dense membrane oxygenators, was only negligibly lower than the concentration in the gas flow into the oxygenator, he postulated that there is no adequate transfer of Isoflurane across the dense membrane.

He investigated wash in of Isoflurane with a constant concentration of 1.0% of Isoflurane in the gas flow into the oxygenator and also wash out with Isoflurane free gas flow into the oxygenator. The limitation of that study consists in the restriction of only measuring concentration differences in the Isoflurane concentration in the gas stream into the oxygenator versus the concentration in the gas stream out of the oxygenator.

The indirect conclusion of Schienagel was that there is no adequate transfer of the anaesthetic agent across the dense membrane type. These data support our observation during the wash in phase using a dense membrane where we could demonstrate no relevant transfer of Sevoflurane and only a retarded and less effective transfer of Isoflurane into the blood.

To our understanding it is not enough to ventilate patients with vapors and consecutively use a dense membrane oxygenator on the CPB and discontinue the application of the anaesthetic vapor as suggested by Prasser.

According to the results of De Hert et al., the duration and timing of administration of volatile anaesthetics seem to correlate with the extend of myocardial protection [14]. After comparison of different anaesthetic protocols in coronary surgery patients, using CPB it could be demonstrated that the cardio protective effects of Sevoflurane as measured by postoperative levels of Troponin1 and indices of myocardial function, were clinically most evident when the volatile anaesthetic was administered throughout the entire period of surgery.

Even during use of a dense membrane oxygenator the concentration of vapors in the blood of the patient are diminished by evaporation and metabolic breakdown in the patient.

To our understanding it is remarkable that there is no certification for oxygenators used for the delivery of vapors on the CPB in North America.

Nevertheless, Carotid Artery Bypass Grafting (CABG) and valve repair have become standard methods in cardiac surgery. World wide about 1,000,000 patients undergo CPB related procedures every year with an increasing percentage of elderly patients with more co-morbidity. Anaesthetic vapors such as Sevoflurane and Isoflurane have shown neuro- and cardio-protective effects and will be used even more widely during CPB. As a result there is a growing need for suitable membranes in oxygenators for the use of vapors on the CPB.

REFERENCES


