

In Vivo Uptake and Elimination of Isoflurane by Different Membrane Oxygenators during Cardiopulmonary Bypass

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Background: Volatile anesthetics are frequently used during cardiopulmonary bypass (CPB) to maintain anesthesia. Uptake and elimination of the volatile agent are dependent on the composition of the oxygenator. This study was designed to evaluate whether the *in vivo* uptake and elimination of isoflurane differs between microporous membrane oxygenators containing a conventional polypropylene (PPL) membrane and oxygenators with a new poly-(4-methyl-1-pentene) (PMP) membrane measuring isoflurane concentrations in blood.

Methods: Twenty-four patients undergoing elective coronary bypass surgery with the aid of CPB were randomly allocated to one of four groups, using either one of two different PPL-membrane oxygenators for CPB or one of two different PMP-membrane oxygenators. During hypothermic CPB, 1% isoflurane in an oxygen-air mixture was added to the oxygenator gas inflow line (gas flow, 3 l/min) for 15 min. Isoflurane concentration was measured in blood and in exhaust gas at the outflow port of the oxygenator. Between-group comparisons were performed for the area under the curve (AUC) during uptake and elimination of the isoflurane blood concentrations, the maximum isoflurane blood concentration (C_{max}), and the exhausted isoflurane concentration (F_E).

Results: The uptake of isoflurane, expressed as AUC of isoflurane blood concentration and a function of F_E , was significantly reduced in PMP oxygenators compared to PPL oxygenators ($P < 0.01$). C_{max} was between 8.5 and 13 times lower in the PMP-membrane oxygenator groups compared to the conventional PPL-membrane oxygenator groups ($P < 0.01$).

Conclusions: The uptake of isoflurane into blood *via* PMP oxygenators during CPB is severely limited. This should be taken into consideration in cases using such devices.

VOLATILE anesthetics are frequently used during cardiopulmonary bypass (CPB) for their anesthetic and vasodilatory effects.^{1,2} Furthermore, isoflurane is assumed to mimic the cardioprotective effects of cardioplegia and ischemic preconditioning *via* an activation of adenosine triphosphate-regulated potassium (K_{ATP}) channels or protein kinase C, particularly in patients with impaired left ventricular function or prolonged periods of aortic cross-clamping.³⁻⁶

To avoid overdosage or underdosage, knowledge about the pharmacokinetics of the volatile agent used and its uptake and elimination depending on the material

of the oxygenator membrane is helpful for anesthetic management. Hemodynamic stability is one of the central tasks during CPB. Overdosage increases the risk of hemodynamic instability with hypotension and a critically low perfusion pressure. In contrast, underdosage may cause hypertension and intraoperative awareness. The use of a microporous polypropylene (PPL) hollow fiber membrane oxygenator is currently standard in a common bypass circuit. Gas transfer rates for oxygen and carbon dioxide, as well as uptake and elimination of volatile agents, are well-known for this type of oxygenator.⁷⁻¹⁰ Recently, a new type of membrane oxygenator has become available, containing a plasma-tight poly-(4-methyl-1-pentene) (PMP) membrane, with the goal to provide a decrease in the generation of microbubbles and blood traumatization during standard CPB and a significant reduction of plasma leakage during long-term application. This membrane is also obtainable with a rheoparin-coated surface. There is only limited information up to now about *in vivo* uptake and elimination of volatile agents by this new oxygenator type. Philipp *et al.*¹¹ measured the isoflurane concentration at the inlet and outlet ports of two PMP oxygenators with an infrared analyzer and found virtually zero transfer of the volatile agent. However, their results must be confirmed by measurements of isoflurane concentrations in blood.

Therefore, this study was designed to compare two different conventional membrane oxygenators with a PPL membrane and two different membrane oxygenators with a PMP membrane, one of them with a rheoparin-coated surface, to evaluate the *in vivo* uptake and elimination of isoflurane during CPB focusing on isoflurane concentrations in blood.

Materials and Methods

After obtaining approval of the Ethics Committee (Regensburg, Germany) and with written informed consent, we studied 24 patients (18 male), aged 36-85 yr (mean age, 62 yr) undergoing elective coronary artery bypass grafting. Patients with significant renal or hepatic impairment, a disposition to malignant hyperthermia, or an ejection fraction of less than 40% were excluded from the study.

Anesthesia was induced with intravenous fentanyl, 5 $\mu\text{g}/\text{kg}$, followed by etomidate until loss of consciousness and pancuronium, 100 $\mu\text{g}/\text{kg}$, and was maintained with an infusion of propofol of 3-5 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, supplemented with bolus doses of fentanyl up to 20 $\mu\text{g}/\text{kg}$ and pancuronium, 50 $\mu\text{g}/\text{kg}$.

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Received from the Department of Anesthesiology, University Hospital, Regensburg, Germany. Submitted for publication October 25, 2001. Accepted for publication February 14, 2002. Supported by the Department of Anesthesiology, University Hospital, Regensburg, Germany.

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A standard CPB technique was used for all patients. Before aortic cannulation, patients were anticoagulated with heparin (375 U/kg). A two-stage cannula was used for drainage of venous blood from the right atrium. The bypass circuit consisted of a roller pump (Stöckert Instruments, Munich, Germany) and a membrane oxygenator.

Four different membrane oxygenators were evaluated, and patients were allocated randomly to one of four groups of six patients each. In group 1, CPB was performed using the CapiroX[®]RX25 oxygenator (Terumo, Tokyo, Japan), and in group 2, CPB was performed using the Hilite[®]7000 (Medos, Stolberg, Germany), both oxygenators with a microporous PPL membrane. In group 3, the Quadrox^D (Jostra, Hirrlingen, Germany) with a plasma-tight PMP membrane was applied, and in group 4, the Hilite[®]7000LT (Medos) with a rheoparin-surfaced plasma-tight PMP membrane was applied.

The circuit was primed with a balanced crystalloid solution and consisted of a hard-shell venous reservoir, open to air. Nonpulsatile pump flow rates of $2.6 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^2 \pm 10\%$ were maintained throughout the test sequence. Alpha stat blood gas management was used for acid-base status control. After aortic cross-clamping and administration of cold cardioplegic solution (Custodiol[®] HTK-Bretschneider; Dr. Franz Köhler Chemie, Alsbach-Hähnlein, Germany), a stable level of perfusion pressure in mild hypothermia (arterial and rectal temperature, 32–33°C) was obtained. These variables remained constant for approximately 10 min before initiating the test sequence. Thereafter, the delivery of 1.0 vol% isoflurane was started *via* a vaporizer (Abbott Laboratories, North Chicago, IL), inserted into the oxygenator's gas supply line, with a constant gas flow of 3 l/min. Washin of isoflurane occurred in all patients during the hypothermic phase with the body temperature maintained stable at 32–33°C. After 15 min, the vaporizer was turned off. Washout of isoflurane took place in the rewarming phase as the temperature increased from 33 to 37°C.

Blood samples for gas chromatography were taken at 0, 15, 30, 45, and 60 s and at 2, 3, 4, 5, 7:30, 10, 12:30 and 15 min in the uptake sequence, and at 1:30, 3, 6, 9, 12, 20, 30, and 45 min in the elimination sequence.

Blood concentrations of isoflurane were measured by gas chromatography-flame ionization detector head space analysis with a Fisons 8000 (ThermoQuest, Eggenbach, Germany) equipped with a heated 50- μl injection loop (Valco, Schenk, Switzerland) and a 30 m \times 0.53 mm ID Supel-Q Plot column (Supelco, Deisenhofen, Germany).¹² Temperatures were kept isothermally at 120°C (oven), 70°C (injector), and 280°C (detector). The carrier gas was He (99.999% pure; Linde, Nuernberg, Germany) used at a constant pressure of 750 mmHg.

The sample preparation consisted of 1 ml heparinized whole blood, which was transferred into a 20-ml head

space vial containing 500 μl distilled water, 100 μl 2-methoxyethanol (Fluka, Buchs, Switzerland) and simultaneously added 10 μl internal standard halothane solution (Sanvital Pharma, Bayerisch Gmain, Germany) in 2-methoxyethanol (10 mM). The vials were immediately capped and shaken for 45 min at 37°C.

Quantification was achieved by preparing exact standard solutions of internal standard halothane and isoflurane in 2-methoxyethanol. One, 5, 10, 25, and 50 μl isoflurane standard solution (11 μM) were added to 99, 95, 90, 75, and 50 μl 2-methoxyethanol and 1 ml gas-free blood drawn from the patient before starting the trial. Also added were 500 μl water and 10 μl internal standard solution to keep identical conditions for the calibration and the measurement. The correlation coefficient of the linear calibration curve was $r^2 > 0.99$, and linearity was given over the whole range of concentration (11–560 μM) with a limit of detection at 3.3 μM . At a spiked level of 57 μM (95% confidence interval, 52.8–61.2), we had a relative recovery rate to internal standard of 100.2%, a within-day coefficient of variation (CV) for the analysis of 5.7% ($n = 5$), and a between-day CV of 9.9% ($n = 24$).

Curves were fitted to uptake and elimination data of the gas chromatography measurements using the software program Kinetica 2000, version 3.0 (InnaPhase, Philadelphia, PA). The curves were fitted by a two-compartment model with a mixed log linear determination of the area under the curve (AUC). AUC for uptake (AUC_{up}) and elimination (AUC_{el}) were calculated for each group. Also calculated were the highest concentrations of isoflurane (C_{max}).

In addition, anesthetic gas concentration was measured with a Datex infrared multiple gas analysis monitor (Capnomac Ultima; Hoyer, Bremen, Germany) next to the gas inlet (F_I) and outlet port (F_E) of the oxygenator, with a sampling flow of 200 ml/min. The gas analysis monitor was calibrated just before starting the trial and was adjusted to zero every time before initiating a measurement. To avoid errors in F_E measurement, the gas outlet port of the oxygenator was not scavenged and was open to the atmosphere *via* a 25-cm-long silicone tube. F_E data from the display screen were noted every minute in the uptake and in the elimination sequence over 30 min.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 software (SPSS, Chicago, IL). Nonparametric tests were used for statistical analysis because the Levene test showed that variances were not homogeneous. Groups were compared using the Kruskal-Wallis test, followed by the test of Tukey and Kramer to detect differences between the groups for AUC_{up}, AUC_{el}, maximum isoflurane blood concentrations (C_{max}), and F_E at 1 and 15 min in the uptake sequence. All data are presented as median (range). A *P* value of 0.05 was regarded as significant.

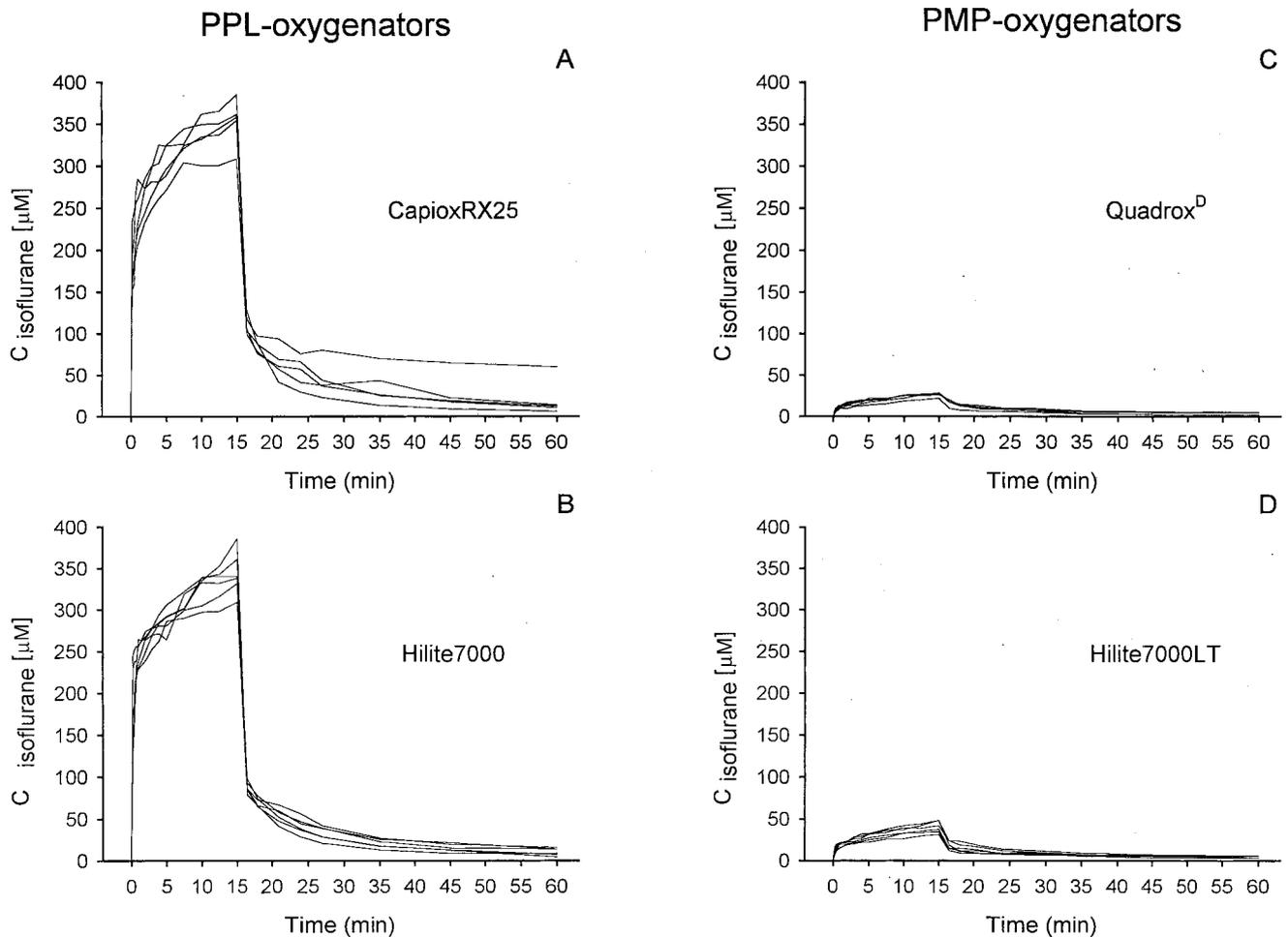


Fig. 1. Isoflurane blood concentrations ($C_{\text{isoflurane}}$ [μM]) for the uptake and elimination sequence in the four oxygenator groups. Each line represents a single patient. (A) Capiox[®]RX25; (B) Hilite[®]7000; (C) Quadrox^D; (D) Hilite[®]7000LT.

Results

The results of AUC_{up} , AUC_{el} , C_{max} , and F_E demonstrated that uptake and elimination of isoflurane by blood were significantly different between the two types of oxygenators.

As displayed in figure 1 and table 1, AUC_{up} (and AUC_{el}) were significantly lower when using a PMP membrane oxygenator compared to a conventional PPL membrane oxygenator ($P < 0.01$). AUC_{up} was 9.6–14.5 times lower with PMP membrane oxygenators compared to PPL membrane oxygenators. The same applied to C_{max} , which was 8.5–13 times lower ($P < 0.01$).

With regard to the F_E data, there was a rapid increase for the two PMP membrane oxygenators, up to 0.94 (0.85–1.0) vol% for the Quadrox^D and 0.88 (0.79–0.97) vol% for the Hilite[®]7000LT after 1 min, reaching a steady state near the administered isoflurane concentration of 1.0 vol% within a few minutes. In contrast, F_E was 0.33 (0.28–0.36) vol% for the Capiox[®]RX25 and 0.31 (0.24–0.43) vol% for the Hilite[®]7000 after 1 min, and steady state was not reached after 15 min of washin (0.61 [0.53–0.67] vol% for the Capiox[®]RX25 and 0.57 [0.45–0.65] vol% for the Hilite[®]7000) as shown in figure 2.

Table 1. Values of AUC_{up} , AUC_{el} , and C_{max} for the Different Oxygenators

	Capiox [®] RX25	Hilite [®] 7000	Quadrox ^D	Hilite [®] 7000LT
AUC_{up} (mm · s)	271.6 (243.8–292.6)*†	266.0 (243.3–274.4)*†	18.8 (13.8–19.6)	27.5 (21.5–31.8)
AUC_{el} (mm · s)	102.2 (77.5–187.5)*†	73.7 (55.8–86.3)*†	15.1 (8.8–22.4)	18.8 (14.1–29.0)
C_{max} (μM)	358.2 (308.8–385.3)*†	336.6 (298.1–385.6)*†	27.6 (22.3–28.5)	39.6 (31.4–48.4)

Data are presented as median (range).

* $P < 0.01$ versus Quadrox^D; † $P < 0.01$ versus Hilite[®]7000LT.

AUC_{up} (mm · s) = area under the curve of the isoflurane blood concentrations in the uptake sequence; AUC_{el} (mm · s) = area under the curve of the isoflurane blood concentrations in the elimination sequence; C_{max} (μM) = maximum isoflurane blood concentration in the four oxygenator groups.

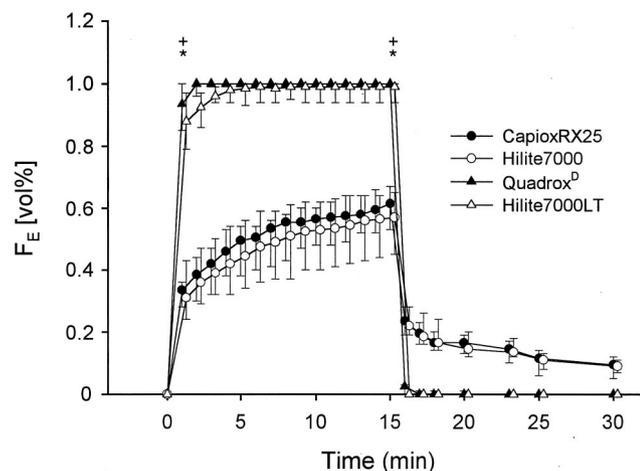


Fig. 2. Exhausted isoflurane concentration (F_E) for the uptake and elimination sequence in the four oxygenator groups. Administered isoflurane concentration (F_I) stayed constant at 1.0 vol% in the uptake sequence; no isoflurane was administered during elimination. Values are presented as median (range). * $P < 0.01$ versus Quadrox^D; + $P < 0.01$ versus Hilite[®]7000LT.

Discussion

The results of the present study demonstrate a markedly decreased uptake of isoflurane *via* PMP membrane oxygenators compared to PPL membrane oxygenators. Uptake and elimination of different volatile agents are well-known for different types of oxygenators.^{7-10,13-15} Microporous PPL hollow fiber membrane oxygenators are commonly used in bypass circuits. The use of these conventional membrane oxygenators can lead to the generation of microbubbles and blood traumatization during standard CPB and plasma leakage, especially during long-term application.¹⁶⁻¹⁸ To avoid these problems, a new type of diffusion membrane oxygenator has recently been developed. The wall of the new plasma-tight hollow fiber consists of a highly porous support matrix and a thin (0.05 μm) tight membrane on the blood side of the matrix. This membrane constitutes a solid barrier between blood and gas and is therefore also described as a solid or diffusion membrane. The homogenous nonporous membrane and the complete separation of blood and gas phases should provide a better biocompatibility with less blood traumatization. Crossing of microbubbles caused by a lowered pressure on the blood side compared to the gas side as well, as plasma leakage should not occur because of the tightness of the membrane. The manufacturer stated an essentially identical gas transfer capability for oxygen and carbon dioxide. Transfer of oxygen was given as 288 ml/min for the Quadrox^D and as 207 ml/min for the Hilite[®]7000LT at 4 l/min blood flow. Transfer of carbon dioxide was reported as 344 ml/min for the Quadrox^D and as 240 ml/min for the Hilite[®]7000LT.^{19,20}

The results of our study demonstrate that the uptake and elimination of isoflurane *via* the new plasma-tight

PMP membrane is markedly reduced compared to conventional PPL membranes. Gas chromatography measurements of isoflurane concentration in blood showed a small but clearly detectable uptake of isoflurane *via* the PMP membranes (fig. 1), which was between 9.6 and 14.5 times lower than the uptake *via* the microporous membranes considering the AUC_{up} (table 1). Likewise, elimination of a small amount of isoflurane by PMP membrane oxygenators could be demonstrated after termination of isoflurane. Our F_E data confirmed the findings of Philipp *et al.*,¹¹ but having knowledge of the blood concentrations, interpretation of the results differs. F_E in the elimination sequence dropped to zero within 1 min for the diffusion membrane oxygenators, suggesting that nearly no uptake of isoflurane has taken place, and therefore, no volatile agent could be exhausted *via* the oxygenator (fig. 2). However, gas chromatography measurement of isoflurane concentration in blood is the more accurate representation of the isoflurane transfer performance, defeating the conclusion of Philipp *et al.*¹¹ that there is zero transfer of isoflurane *via* the new PMP membrane.

According to Mets,^{21,22} the effect of CPB with cooling on the uptake of volatile anesthetics administered to the oxygenator is dependent on three main factors:

1. the blood-gas (B-G) solubility of the agent and the opposing effects of cooling in increasing B-G solubility of blood *versus* hemodilution, which decreases B-G solubility of volatile anesthetic agents
2. the increased solubility in tissue of volatile anesthetics secondary to hypothermia
3. uptake by the oxygenator

Furthermore, altered blood flow distribution or hypotension during CPB might be minor factors that could affect gas transfer under these circumstances.²¹

Free diffusion of gas molecules through the micropores of the capillaries is the principle of gas exchange *via* conventional PPL membrane oxygenators. The driving force of gas transfer is the difference in partial pressure of oxygen, carbon dioxide, and the used volatile agent between the gas and the blood side of the membrane. In contrast, the gas exchange *via* PMP membranes imitates the physiologic principle of diffusion of gas molecules through tight gas-permeable cell membranes. Gas transfer *via* the solid layer is a process of solubility and diffusion depending on partial pressure gradients and the specific gas permeabilities of the membrane. Whether rheoparin coating influences the gas exchange especially for isoflurane is not known.

According to Nunes,²³ the simplest model used to explain and predict gas permeation through nonporous polymers is the solution-diffusion model. It is assumed that the gas at the high-pressure side of the membrane dissolves in the polymer and diffuses down a concentration gradient to the low-pressure side, where the gas is

desorbed. The combination of the laws of solubility and diffusion of Henry and Fick leads to the equation:

$$J = \frac{D \cdot S \cdot \Delta p}{l} = \frac{P \cdot \Delta p}{l}$$

where J is the rate of diffusion per unit area, D is the diffusion coefficient of the gas in the polymer, S is gas solubility, Δp is the partial pressure coefficient, P is the permeability coefficient, and l is membrane thickness.

The diffusion coefficient D is constant for a particular gas and diffusion barrier material at a constant temperature and always decreases with increasing size of the molecule. On the other hand, the solubility of gases generally increases with molecular size because the intermolecular forces between gas and polymer increase. Corresponding to this model, a possible explanation for the extremely reduced uptake of isoflurane by diffusion membrane oxygenators could be a very low diffusion coefficient of isoflurane in the solid layer of the new membrane because of its molecular size, considering that glassy polymers as PMP usually show a preferred permeability to smaller molecules.²³ However, the diffusion coefficient for isoflurane-PMP and solubility of isoflurane in PMP is not known and should be the topic of further investigations.

Stern *et al.*²⁴ described a delay in uptake and elimination of isoflurane by the Scimed membrane oxygenator due to a high affinity of the silicone membrane for isoflurane. Large amounts of isoflurane were absorbed by the oxygenator and were not transferred into the blood. The possibility that PMP membranes absorb large amounts of the volatile agent is improbable and is not supported by our data; therefore, we did not apply the study design of Stern. F_E for the two PMP oxygenators at 1 min in the washin sequence was almost equal to F_I at the inflow line of the oxygenator. Therefore, if greater amounts of isoflurane would have been absorbed by the PMP membrane, F_E should have been clearly lowered.

The assumption that the rheoparin coating of the new membrane influences the uptake of isoflurane must be discarded as there are no significant differences between the two PMP oxygenators in regard to AUC_{up} and C_{max} . Membrane material of both PMP oxygenators is provided by the same and only manufacturer of this membrane worldwide (Membrana GmbH, Wuppertal, Germany). Our data indicate that the membrane material itself is responsible for the decreased uptake of isoflurane.

While the explanation of our results may be speculative, the results of our study have important clinical implications. Due to the significant differences in isoflurane transfer characteristics of the new membrane, the clinician must consider the composition of the bypass circuit and in particular the composition of the incorporated oxygenator. According to Rosen *et al.*,²⁵ there is a

need for greater awareness about CPB circuit composition, and circuits should be individually examined for drug interactions. In addition, the failure of the new PMP oxygenators to eliminate isoflurane inhaled before CPB may affect some clinicians' practices. As far as we know, the two PMP oxygenators we examined are the only ones currently obtainable. To ascertain whether a volatile agent is being delivered to the patient, measurements of the gas concentrations at the inflow and outflow ports of the oxygenator with a conventional gas analyzer may provide valuable information but do not necessarily reflect blood concentrations. Therefore, it should be clearly stated on every type of oxygenator whether or not it is suitable for administration of volatile agents.

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