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Original Article

Elimination of sevoflurane is reduced in plasma-tight compared to conventional membrane oxygenators

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Summary

Background and objective: It has been demonstrated that volatile anaesthetics have cardioprotective properties during open-heart procedures, especially when administered continuously. European Council Directive 93/42/EEC concerning medical devices bans the supplementary incorporation of anaesthetic vaporizers in the bypass circuit. Since the uptake of volatile anaesthetics via diffusion membrane oxygenators is severely reduced, it is hypothesized that clinically relevant concentrations of sevoflurane will remain in the patients' blood following saturation with a volatile agent before start of cardiopulmonary bypass. This study was designed to compare conventional and diffusion membrane oxygenators regarding their *in vivo* elimination of sevoflurane. *Methods:* Twenty patients undergoing elective coronary bypass surgery were randomly allocated to two groups, either using a conventional polypropylene membrane oxygenator or a plasma-tight poly-(4-methyl-1-pentene) membrane oxygenator in a miniaturized extracorporeal circuit. Anaesthesia was maintained with sevoflurane, which was stopped at the start of cardiopulmonary bypass. During cardiopulmonary bypass, sevoflurane concentration was measured in blood and in the exhausted gas from the oxygenator. *Results:* The elimination of sevoflurane, expressed as the relative blood concentration, was significantly increased in polypropylene membrane oxygenators compared to poly-(4-methyl-1-pentene) membrane oxygenators. This resulted in an approximately threefold higher sevoflurane blood concentration in the poly-(4-methyl-1-pentene) group over the course of cardiopulmonary bypass. *Conclusions:* With the incorporation of a poly-(4-methyl-1-pentene) oxygenator in a miniaturized bypass circuit, relevant concentrations of a previously applied volatile agent can be maintained even without further supply throughout cardiopulmonary bypass. This might be an alternative approach to cardioprotection when sevoflurane cannot be administered through cardiopulmonary bypass.

Keywords: CARDIAC SURGICAL PROCEDURES; EXTRACORPOREAL CIRCULATION; REPERFUSIN INJURY; SEVOFLURANE; OXYGENATORS; MEMBRANE.

Introduction

Recently published studies have clearly demonstrated that volatile anaesthetics can protect the myocardium from ischaemia and reperfusion injury during open-heart procedures, resulting in lower postoperative troponin I release and improved postoperative cardiac function when compared with a total intravenous (i.v.) anaesthetic regimen. These cardioprotective effects were clinically most apparent when the volatile anaesthetic was administered throughout the entire surgical procedure [1].

However, the European Community Council Directive 93/42/EEC concerning medical devices, dated 14 June 1993 [2], makes administration of

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volatile anaesthetics during cardiopulmonary bypass (CPB) difficult. The directive bans the supplementary incorporation of an anaesthetic vaporizer into the extracorporeal circuit since this would add complementary safety and performance-related device features. Consequently, several hospitals in Germany have removed vaporizers from their extracorporeal circuits. They now use i.v. anaesthetics for maintenance of anaesthesia during CPB, despite the fact, that some of these drugs have been shown to neutralize the cardioprotective properties of volatile anaesthetic agents [3].

As recently demonstrated by our study group, the uptake of volatile anaesthetics via a diffusion membrane oxygenator containing a plasma-tight poly-(4-methyl-1-pentene) (PMP) membrane is severely reduced [4]. There is only limited information on *in vivo* elimination of volatile anaesthetics by PMP oxygenators following the saturation with a volatile agent before CPB. However, it could be hypothesized that, when using a diffusion membrane oxygenator, clinically relevant blood concentrations of sevoflurane would be maintained until the end of CPB following administration of the volatile agent until the initiation of extracorporeal circulation (ECC). Depending on the remaining sevoflurane concentration, cardioprotective properties might still be exerted.

The present study was designed to compare the *in vivo* elimination of sevoflurane during miniaturized extracorporeal circulation with two different membrane oxygenators, one with a conventional microporous polypropylene (PPL) hollow fibre membrane and one with a new plasma-tight PMP membrane. Sevoflurane was given prior to CPB only. Blood concentrations of sevoflurane were measured repeatedly during CPB by gas chromatography and the area under the curve (AUC) was calculated.

Methods

After obtaining approval of the local Ethics Committee (Regensburg, Germany) and with written informed consent, we studied 20 patients (17 males), aged 45–83 yr (mean age, 64 yr) undergoing elective coronary artery bypass grafting. Patients with a history of renal or hepatic impairment, a disposition to malignant hyperthermia, a relevant aortic valve insufficiency, a body mass index $>40\,kg\,m^{-2}$ or an ejection fraction less than 40% were excluded from the study.

Patients were randomly allocated either to group PPL, in which CPB was performed using an oxygenator with a conventional microporous (PPL) membrane (Highlite 7000; Medos, Stolberg, Germany), or to group PMP, in which CPB was performed with a plasma-tight PMP membrane oxygenator (Quadrox D; Jostra, Hirlingen, Germany). Patients were randomly allocated to one of the two groups by a computer-generated sequence.

Anaesthesia was induced in all patients with i.v. fentanyl (Janssen-Cilag GmbH, Neuss, Germany) 5–10 $\mu g\,kg^{-1}$, followed by etomidate (B. Braun Melsungen AG, Melsungen, Germany) until loss of consciousness and pancuronium (Curamed Pharma GmbH, Karlsruhe, Germany), 100 $\mu g\,kg^{-1}$. Anaesthesia was maintained with 1.7% end-expiratory sevoflurane (Abbott GmbH, Wiesbaden, Germany), supplemented with bolus doses of fentanyl up to 10 $\mu g\,kg^{-1}$ and pancuronium, 25 $\mu g\,kg^{-1}$. With initiation of the ECC the ventilation and the supply of the volatile agent was stopped; anaesthesia was maintained by continuous infusion of propofol (Astra Zeneca GmbH, Wedel, Germany) at 6–8 $mg\,kg^{-1}\,h^{-1}$.

CPB was performed using a miniaturized extracorporeal circulation (MECC) system (MECC System, Jostra AG, Hirlingen, Germany), which has previously been described in detail by Wiesenack and colleagues [5]. MECC is a closed, fully heparin-coated (Bioline Coating, Jostra AG) and pre-connected ECC-system, consisting of a membrane oxygenator and a centrifugal pump (RotaFlow, Jostra AG), a two-stage venous cannula (40–32 Fr), an aortic cannula (7 mm) and 3/8" polyvinyl chloride (PVC) tubing (180 cm). A non-pulsatile flow rate up to $2.5\,L\,min^{-1}\,m^{-2} \pm 10\%$ was delivered. The reduced tubing length and the absence of a venous reservoir and cardiotomy suction prevented any air–blood contact and allowed a reduced priming volume of about 550 mL (350 mL of Ringer's solution and 200 mL of mannitol 20%). Mild hypothermia to a rectal temperature of 33–34°C was induced during bypass with the heat exchanger incorporated in the oxygenator. Rewarming of the patient was easily achieved. Before initiating MECC, heparin 150 $IU\,kg^{-1}$ was given. The target activated clotting time (ACT) was 250–300 s. A cell-saving device was used for blood salvaging from the surgical field. The centrifuged and washed blood was retransfused at the end of surgery.

Antegrade blood cardioplegia, as described by Calafiore and colleagues [6], was delivered intermittently via an aortic root cannula with vent line and pressure tubing (DLP; Medtronic, Minneapolis, MN, USA). The same surgeons, anaesthesiologists and perfusionists were involved in both groups of patients.

Blood sampling and measurement of sevoflurane

Blood samples for gas chromatography were taken at 20, 15, 10 and 5 min before start of MECC from

the central venous line to verify a constant blood concentration of sevoflurane. The mean values were regarded as the 100% reference level in the respective groups. After start of MECC, blood was sampled from the shunt line of the MECC system at the following time points: 30 and 90 s, and 3, 5, 7, 9, 12, 15, 20, 30, 40, 50, 60, 70 min. The initial close sampling was chosen due to the expected rapid decline of the sevoflurane blood concentration following initiation of CPB. Some patients could not be studied after time point '50 min' due to the variable length of cross-clamp time. The sevoflurane blood concentrations (C_{rel}) during the elimination phase were expressed as percentages of the pre-MECC levels. Each case was fitted into a two-compartment model by the WinNonlin Professional software (Mountain View, CA, USA).

Blood concentrations of sevoflurane were measured by gas chromatography-flame ionization detector head space analysis with a Fisons 8000 (ThermoQuest, Egelsbach, Germany) equipped with a heated 50 μL injection loop (Valco, Schenkon, Switzerland) and a 30 m × 0.53 mm ID Supel-Q Plot column (Supelco, Deisenhofen, Germany). Temperatures were kept isothermically at 120°C (oven), 70°C (injector) and 280°C (detector). The carrier gas was Helium (99.999% pure; Linde, Nuernberg, Germany) used at a constant pressure of 85 kPa.

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 μL). 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 (about 20 $\mu mol\,mL^{-1}$ each). Sevoflurane standard solutions of 1, 5, 10, 25 and 50 μL were added to 49, 45, 40, 25 and 0 μL 2-methoxyethanol and 1 mL anaesthetic-free blood was drawn from the patient before starting the trial. Also, 500 μL water and 10 μL internal standard halothane solution were added to keep identical conditions for calibration and measurement. The correlation coefficient of the linear calibration curve was $r^2 > 0.99$, and linearity was given over the whole range of concentration with a detection limit at 6.0 $\mu mol\,L^{-1}$. Curves were fitted to elimination data of gas chromatography measurements using a two-compartment model of the software program WinNonlin Professional, version 4.1.

Exhaust anaesthetic gas concentration from the MECC system (F_E) was measured with a Datex infrared multiple gas analysis monitor (Capnomac Ultima; Hoyer, Bremen, Germany) next to the gas outlet port of the oxygenator, with a sampling flow of 200 $mL\,min^{-1}$. Directly before starting a trial, the gas analysis monitor was calibrated and adjusted to zero each time a measurement was initiated. 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 silicone tube. Values were registered at the same time as the blood samples were obtained from the MECC.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 software (SPSS, Chicago, IL, USA). Non-parametric tests were used for statistical analysis because the Lilliefors modification of the Kolmogorov–Smirnov test showed that both original and log-transformed data were not normally distributed. Groups were compared using the *U*-test to detect differences between groups for the AUC at 60 min and the sevoflurane blood concentrations in the elimination sequence. All data are presented as mean ± SD. A *P*-value <0.05 was regarded as significant.

Results

The two groups did not differ with respect to patient characteristics or perioperative data (Table 1). The mean peak blood concentrations of sevoflurane before initiation of the MECC reached comparable levels in both groups (434 ± 115 $nmol\,g^{-1}$ in group PMP, and 415 ± 133 $nmol\,g^{-1}$ in group PPL). Both groups

Table 1. Patient characteristics and perioperative data.

	Group PMP	Group PPL
Age (yr)	60.4 ± 8.9	68.2 ± 10.8
Gender (M/F)	8/2	9/1
BMI ($kg\,m^{-2}$)	29.7 ± 2.5	27.5 ± 2.8
EF (%)	57.9 ± 13.7	61.4 ± 13.3
Grafts (*n*)	3.7 ± 0.9	3.7 ± 1.0
Cross-clamp-time (min)	67.5 ± 15.0	58.3 ± 30.0
CPB time (min)	100.2 ± 20.7	92.3 ± 34.6
Postoperative ventilation (h)	11.5 (4–24)	10.5 (0–126)
ICU stay (days)	1 (0–4)	1 (0–7)
Hospital stay (days)	10 (6–21)	11 (7–24)

BMI: body mass index; EF: ejection fraction; CPB: cardiopulmonary bypass; ICU: intensive care unit; PMP: poly-(4-methyl-1-pentene); PPL: polypropylene.
Data are presented as mean ± SD, median (range), or numbers of patients.

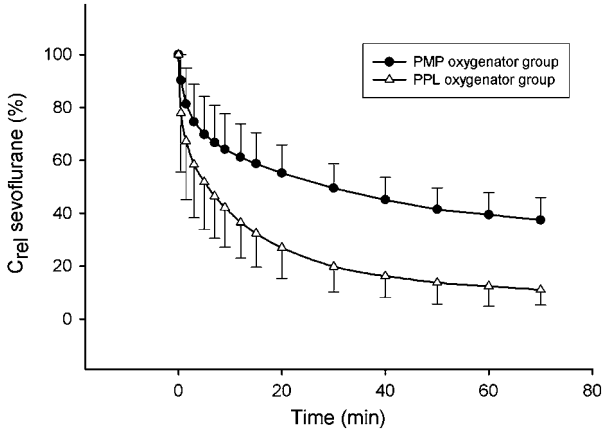

Figure 1.
Elimination of sevoflurane during minimal extracorporeal circulation (MECC). Relative decrease in sevoflurane blood concentration (C_{rel}) after start of cardiopulmonary bypass with polypropylene membrane oxygenators (PPL) and poly-(4-methyl-1-pentene) membrane oxygenators (PMP). The blood concentration immediately before initiation of MECC is set to 100%. The difference between the groups is significant from the fifth minute on. Data are presented as mean ± SD.

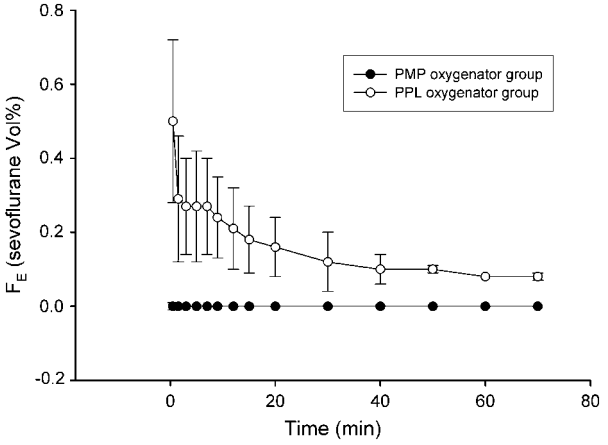

Figure 2.
Sevoflurane concentration in the oxygenator gas exhaust. Sevoflurane concentration measured at the outlet port of the oxygenator. Washout of sevoflurane was demonstrated in the polypropylene membrane oxygenator (PPL) group. There was no measurable washout in the poly-(4-methyl-1-pentene) membrane oxygenator (PMP) group. Data are presented as mean ± SD.

showed a drop in C_{rel} from start of CPB, with a faster decrease in the PPL group compared to the PMP group (Fig. 1). The AUC at 60 min was significantly different between the two types of oxygenators ($AUC_{PMP} = 3193 \pm 625\%$ min vs. $AUC_{PPL} = 1689 \pm 755\%$ min, $P < 0.05$). From the fifth minute on, the difference in sevoflurane blood concentration was statistically significant ($P < 0.05$).

As shown in Figure 1, virtual declamping at time points 30, 40, 50 and 60 min would result in average sevoflurane blood concentrations of 49%, 45%, 41% and 39% for the PMP group and in approximately threefold lower concentrations of 20%, 16%, 14% and 12% for the PPL group in relation to the point of reference at the start of the CPB.

With regard to the F_E data, there was a significant efflux of sevoflurane between 0.2 and 0.5 vol% at the oxygenators' exhaust gas outlet for the first few minutes in the PPL group, reaching a steady state with a mean efflux of about 0.1 vol% within 30 min. In contrast, F_E in the PMP group remained zero, suggesting that no measurable amount of volatile agent had been lost via the oxygenator exhaust (Fig. 2).

Discussion

Our study demonstrates a markedly increased elimination of sevoflurane via PPL membrane oxygenators compared to PMP membrane oxygenators in a miniaturized bypass circuit during coronary artery bypass grafting (CABG) procedure. Thus, the hypothesis that significantly higher concentrations of sevoflurane remain in patients' blood using an oxygenator with a plasma-tight membrane was confirmed.

Diffusion membrane oxygenators have primarily been developed to avoid well-known problems regularly appearing when using conventional microporous PPL hollow fibre membrane oxygenators such as the generation of microbubbles, blood trauma during CPB or plasma leakage during long-term application. The wall of the plasma-tight PMP membrane consists 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 blood and gas. The homogenous tight membrane and the complete separation of blood and gas phases obviously provide a better biocompatibility with less blood trauma. Crossing of microbubbles caused by lowered pressure on the blood side compared to the gas side, as well as plasma leakage does not occur because of the tightness of the membrane. Unfortunately, the uptake of isoflurane into blood via PMP oxygenators during CPB is severely limited, as recently demonstrated by our study group [4]. Considering that glassy polymers such as PMP usually show a preferred permeability to smaller molecules, this effect may be caused by a very low diffusion coefficient of the volatile agent in the solid layer of the plasma-tight membrane due to its high molecular size.

During the first 5 min of CPB, we found rapidly decreasing relative blood concentrations of

sevoflurane in both groups. This can mainly be assigned to three phenomena:

1. dilution by the priming volume of the MECC at start of CPB,
2. ongoing re-distribution from the central blood compartment into tissue without further supply of the volatile agent, and
3. uptake of the volatile anaesthetic into the PVC tubing material of the MECC.

The reduced priming volume of the MECC of just 550 mL and the use of small volume cardioplegia certainly diminishes the effect of dilution compared to conventional ECC, normally using priming volumes up to 1500 mL.

The ongoing distribution of sevoflurane from the central blood department into a second tissue compartment can be assumed to be comparable in both groups and independent of the use of a particular oxygenator.

The uptake of the volatile anaesthetics into the PVC of the MECC tubing could not be quantified in this investigation. *In vitro* data by Suzuki and colleagues [7], indicate a loss of volatile anaesthetics in PVC tubing. However, due to a 200-fold higher blood flow and the higher circulating blood volume these findings may only play a minor role in our clinical setting. Therefore, despite the reduced priming volume of the MECC, the rapid decrease of sevoflurane blood concentration in both groups should mainly be attributed to the initial effect of dilution and to a lesser degree to distribution and loss.

In the further course of CPB, there was a threefold lower relative blood concentration of sevoflurane in the PPL group compared to the PMP group (Fig. 1). This is most likely related to a relevant loss of sevoflurane through the microporous membrane of the PPL oxygenator into the exhausted gas (Fig. 2). A significant efflux of sevoflurane at the oxygenators exhaust gas outlet was detected in the PPL group, while no measurable amount of sevoflurane was exhausted via the PMP oxygenator.

The decrease of volatile agent in the PMP group still detectable can mainly be explained by distribution.

According to the results of De Hert and colleagues [1,8], the duration and timing of administration of volatile anaesthetics seem to correlate with the extent of myocardial protection. They compared different anaesthetic protocols in patients undergoing coronary surgery with CPB and found that the cardioprotective effects of sevoflurane, as evidenced by postoperative levels of troponin I and indices of myocardial function, were clinically most apparent when the volatile anaesthetic was administered throughout the entire period of surgery [1]. Against that background and the Directive of the Council of the European Community, banning the incorporation of anaesthetic vaporizers in the CPB circuit, the findings of our investigation become important. Our results indicate that relevant concentrations of a previously applied volatile agent can be maintained during MECC with a PMP membrane oxygenator, even without continued administration from a vaporizer in the bypass circuit. Since some i.v. agents may potentially neutralize the cardioprotective effects of inhalational agents [3,9], patients should benefit from an exclusive volatile anaesthetic without i.v. supplementation. Whether the residual sevoflurane concentrations in our patients are sufficient for a cardioprotective effect remains unanswered and this constitutes a limitation of this investigation.

Our data suggest that the incorporation of a PMP membrane oxygenator in a miniaturized closed bypass circuit in order to reduce the elimination of previously administered volatile anaesthetics could be an interesting approach to cardioprotection when continuous administration is not possible because of the European Community Council Directive, banning the supplementary incorporation of an anaesthetic vaporizer in the bypass circuit. Additional studies are required to confirm our findings and to demonstrate the possible beneficial effects of this approach in cardiac surgical patients.

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