SHORT COMMUNICATON

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The equilibrated blood sevoflurane concentrations show a rapid decrease after switching from ventilation for the human lung to cardiopulmonary bypass

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ABSTRACT

Volatile anesthetics (VAs) protect myocardial cells during cardiovascular surgeries, including cardiopulmonary bypass (CPB). In CPB, blood is gradually transferred from the body to a CPB unit until the target cardiac index is achieved, following which human lung (HL) ventilation is stopped. This pilot study aimed to evaluate changes in the blood sevoflurane concentrations 5 min after the start of CPB when its delivery to the oxygenator began after HL ventilation with sevoflurane was completed. Six patients were recruited and participated in this study. For each patient, the equilibrated blood sample, collected 20 min after starting the delivery of 1.7% sevoflurane (HL group), and another blood sample, collected 5 min after starting the CPB, were analyzed using gas chromatography equipped with a flame ionization detector. The mean (± standard deviation) sevoflurane concentrations in the HL and 5 min after starting CPB groups were 58.6 ± 4.7 and 14.5 ± 5.0 μg/ml, respectively ($P < 0.01$). In conclusion, the equilibrated blood sevoflurane concentrations showed a rapid decrease when switching from sevoflurane ventilation for the HL to CPB unless it was introduced to the oxygenator until completion of the switch.

Keywords: cardiopulmonary bypass, sevoflurane, blood concentration, oxygenator, human lung ventilation

Abbreviations:
VA: volatile anesthetic
CPB: cardiopulmonary bypass
HL: human lung
PSI: patient state index
n: number of patients
SD: standard deviation
vs: versus

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INTRODUCTION

Volatile anesthetics (VAs) are recommended by several guidelines for use during cardiovascular surgeries, including cardiopulmonary bypass (CPB), to protect the cardiomyocytes during these surgeries.[1,2] In a CPB, blood is gradually transferred from the body to the CPB unit until the target cardiac index is attained, and then the human lung (HL) ventilation is stopped. Generally, VAs are delivered to the oxygenator from an independent vaporizer attached to the CPB system or the anesthesia machine vaporizer. In the latter case, which is commonly performed in most Japanese facilities, VA delivery to the oxygenator begins after the completion of HL ventilation with VAs (Figure 1). We hypothesized that the conversion operation from ventilation for HL to CPB would change the blood VA concentrations. A sharp fall in the blood VA concentration after the start of CPB can result in intraoperative awakening, which can be a serious issue. Therefore, it is important to monitor changes in the blood VA concentration after switching to CPB when using the anesthesia machine vaporizer. We conducted a pilot study to evaluate blood sevoflurane concentration at 5 min after the start of CPB.

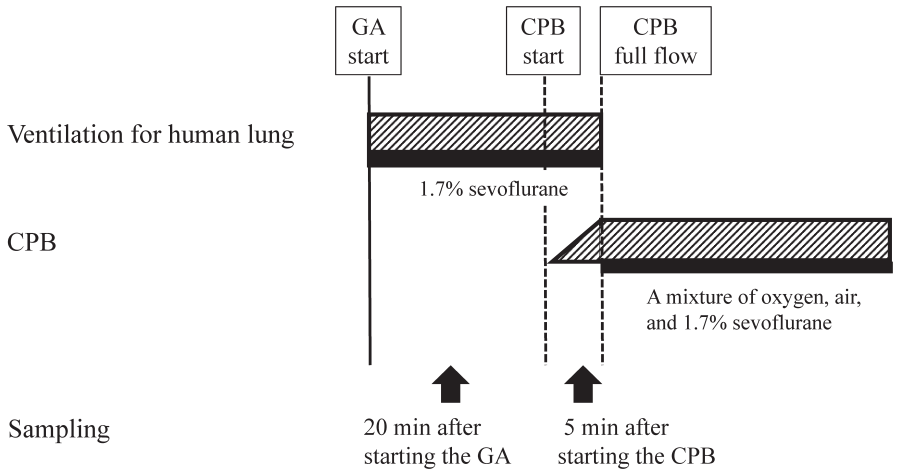

Fig. 1 Gas flow to the patient and blood sampling points
In human lung (HL) ventilation, 1.7% sevoflurane was simultaneously introduced to induce general anesthesia (GA). Sevoflurane delivery to the oxygenator begins after the completion of HL ventilation. In this study, the time required to complete the conversion to cardio-pulmonary bypass (CPB) was within 8 min in all cases. For each patient, the equilibrated blood sample was collected 20 min after starting the GA. Another blood sample was collected 5 min after starting the CPB.

METHODS

This study was registered with the University Hospital Medical Information Network (Study ID: UMIN000033710) and approved by the Institutional Review Board of the Nagoya University Hospital (IRB #2018–0329). Patients aged 20–90 years who were scheduled for elective cardiac surgery with CPB between January and August 2019 were recruited with the similar eligibility criteria to our previous study.[3] Patients with contraindications for VA use, such as those with malignant hyperthermia and significant renal or hepatic impairment, were excluded.

The methods for general anesthesia, blood sampling, and measurement of blood sevoflurane

concentrations using gas chromatography equipped with a flame ionization detector have been reported previously.[3] A regional oximetry monitor for the brain and a radial artery cannula for monitoring and sampling blood pressure were used in all patients. Fentanyl, remifentanil, rocuronium, and midazolam were administered to induce general anesthesia, which was maintained using 1.7 vol% sevoflurane and air-oxygen mixture administered at a total flow rate of 3.0 l/min. Porcine heparin (300 U/kg) and additional heparin bolus (50 U/kg) were injected to maintain an activated clotting time of at least 450 s. The non-pulsatile pump was maintained at a flow rate of 2.6 l/min/m^2 ± 10%. When the target flow rate was achieved, ventilation was stopped; thereafter, the delivery of 1.7 vol% sevoflurane was started through a vaporizer (D-Vaper 3000, Dräger Medical Japan Ltd., Tokyo, Japan), using the gas supply line of the oxygenator, with a constant gas mixture of oxygen and air (F_IO_2: 50%–60%) at a flow rate 0.5–3.0 l/min. The concentration of anesthetic gas in each oxygenator was monitored using an anesthesia machine (Perseus A500, Dräger Medical Japan Ltd). A drainage system was used to limit VA leakage during CPB.[4,5]

One blood sample was collected from each patient using a radial artery cannula system with a closed circuit for blood sampling (Tru Wave with VAMP system, Edwards Lifesciences Co., Ltd., Irvine, CA). To measure blood concentrations of sevoflurane, blood samples (0.5 ml) were collected in a saline-containing vial sealed with a rubber cap and an aluminum crimp seal (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). For each patient, the equilibrated blood sample was collected 20 min after starting the delivery of 1.7% sevoflurane with tracheal intubation and 3.0 l/min of total gas flow (the HL group). Another blood sample was collected 5 min after starting the CPB and keeping the ventilation on, using a mixture of oxygen, air, and 1.7% sevoflurane at 3.0 l/min (the 5 min after starting CPB group). Sevoflurane delivery to the oxygenator was started after the HL ventilation was completed (Figure 1). In this study, we used four types of oxygenators manufactured by Terumo Corporation, LivaNova Japan K.K., Medtronic Japan Co. Ltd., and SENKO MEDICAL INSTRUMENT Mfg. Co. Ltd. (all manufacturers: Tokyo, Japan), and there was no demonstrable functional difference between them.[3] To prevent intraoperative awakening, the patient state index (PSI) was monitored using the RD SedLine® EEG sensor (Masimo Japan, Tokyo, Japan), and we prepared to administer midazolam (0.02–0.04 mg/kg) when the PSI exceeded 60.

The sample size was calculated for over five samples based on the quality control of gas chromatography ≤ 15%, coefficient of variation ≤ 10%, and sample sizes and variability in blood sevoflurane concentrations in the drug interview forms.[6] The patient information and blood concentration data were expressed as mean ± standard deviation (SD). As the primary endpoint of this study, changes in blood sevoflurane concentrations between the HL and 5 min after starting CPB groups were analyzed using the paired t-test. A p-value < 0.05 indicated statistical significance. All data were analyzed using SPSS software (version 27, IBM Japan Ltd., Tokyo, Japan).

RESULTS

After obtaining written informed consent from the patients, six patients were assessed for eligibility and recruited for the study. In each patient, two samples (for the HL and 5-min after starting CPB groups) were collected and totally 12 samples were analyzed. None of the patients withdrew from the study. All six patients were men and their mean age, height, weight, and body mass index were 63.6 ± 20.5 years, 168.0 ± 2.9 cm, 64.9 ± 9.9 kg, and 23.0 ± 3.6 kg/m^2, respectively. While three of the patients underwent coronary bypass graft, the other three

underwent valve surgery. The mean sevoflurane concentrations for the HL (58.6 ± 4.7 μg/ml) and 5 min after starting CPB (14.5 ± 5.0 μg/ml) groups were significantly different ($p < 0.01$) (Figure 2). None of the patients had an intraoperative awakening or required midazolam administration.

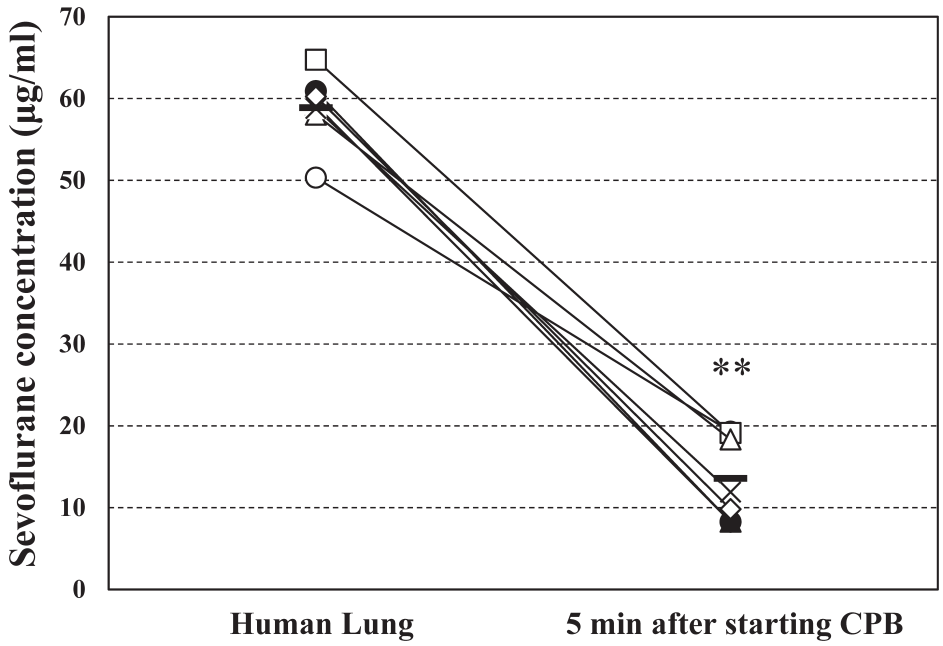

Fig. 2 Blood sevoflurane concentrations
Blood samples were collected at 20 min in the human lung group and 5 min after starting the delivery of 1.7% sevoflurane to the oxygenator group. Plots and horizontal lines at each point on the horizontal axis correspond to the measured (n = 6) and mean values, respectively, of the blood sevoflurane concentrations.
** $p < 0.01$ vs Human lung (paired t-test).

DISCUSSION

The most important finding of our study was that blood sevoflurane concentrations that were equilibrated by ventilation with 1.7% sevoflurane could not be maintained after switching to CPB, even if lung ventilation with sevoflurane continued during the switch. The blood sevoflurane concentration 5 min after starting the conversion decreased to approximately 25% of the HL level. The decrease was comparable to that seen after discontinuing inhalation, as reported in the sevoflurane interview form.[6] Factors affecting blood VA concentrations during conversion to CPB included blood cooling, hemodilution by CPB priming, changes in blood flow distribution, volatilization from venous reservoirs and surgical fields, and hypotension.[7,8] Although it might be important to determine factors that have the most impact, this clarification does not seem meaningful as the degree of decrease was comparable to sevoflurane pharmacokinetics. In addition, in this study, the time required to complete the conversion to CPB was within 8 min in all cases. As described in the interview form,[6] the mean awakening time to respond to the call was 9.88 min when sevoflurane was used with an average maintenance concentration of 1.59%. Furthermore, it is reported that minimum alveolar concentration (MAC)-awake value of

sevoflurane is about one-third of MAC value of 1.7%,[9] which is the MAC value at about 60 years old[10] and is used in this study. Taking these evidences into consideration, it is suggested that sevoflurane anesthesia alone, as in this study, results in insufficient sedation and an increased possibility of intraoperative awakening. However, there were no cases of intraoperative awakening or requirement for midazolam administration in this study. During the conversion time of 8 min, the median PSI was 37 (interquartile range: 34–42). In addition, we confirmed that blood sevoflurane concentrations recovered to the equilibrated HL ventilation level at 20 min after switching to CPB.[3] Our findings, therefore, highlight the need for a safer sevoflurane induction method, which is different from ours, when switching from sevoflurane ventilation for HL to an oxygenator.

Here, we propose ways to prevent the intraoperative awakening during sevoflurane anesthesia associated with CPB switching. One of the best approaches is to introduce a mixture of oxygen and VA into the oxygenator immediately after starting CPB. It would be convenient if a vaporizer dedicated to the oxygenator is connected in addition to the one for HL ventilation. In Nitzschke's report,[11-13] blood sevoflurane concentration decreased to 79% of the equilibrated HL value at 2 min after starting CPB, but immediately returned to 88% at 7 min and then stabilized. However, in Japan, several facilities do not have such dedicated equipment. Alternatively, if there is only one vaporizer available, it would be better to connect the gas distributor to the external port of the anesthesia machine for simultaneous HL ventilation and introduction into the oxygenator.

Nevertheless, as such operations are impossible with the current anesthesia machines, improvement in the equipment is desired. Alternatively, the oxygenator can be connected with the vaporizer immediately after switching to CPB and supply oxygen to the patient's lungs using a bag-valve-mask, such as the Jackson-Rees. In clinical practice, the administration of narcotic analgesics and muscle relaxants such as fentanyl, remifentanil, and rocuronium, which were used in this study, could prevent awakening for a while. However, the longer it takes to reach full flow, the higher the risk of intraoperative awakening. Even with these improvements in equipment and procedures, we believe PSI monitoring and preparation for the administration of sedatives such as midazolam would further improve the outcomes. Further studies are needed to investigate the relationship between the blood concentration of sevoflurane and anesthesia-related monitoring values before, during, and after switching to CPB.

In conclusion, in CPB surgeries under sevoflurane anesthesia, the equilibrated blood concentration of the VA rapidly decreased when switching from sevoflurane ventilation for the HL to CPB unless sevoflurane was introduced to oxygenator until switch completion.

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DISCLOSURE STATEMENT

None of the authors have any conflicts of interest to declare in relation to this work.

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