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SHORT COMMUNICATION

Effect of decreased fetal perfusion on placental clearance of volatile anesthetics in a dual perfused human placental cotyledon model

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Abstract Placental transfer of volatile anesthetics is a critical issue in managing fetal distress during cesarean section under general anesthesia. Using dual perfused human placental cotyledons obtained from parturients undergoing elective cesarean section ($n = 5$), we investigated the effect of decreased fetal perfusion on placental clearance of sevoflurane and isoflurane. Keeping the maternal flow rate fixed, fetal flow rate was consecutively decreased from 3 ml/min (control perfusion) to 2 ml/min (intermediate perfusion) and to 1 ml/min (hypoperfusion). Placental transfer was assessed by the clearance of anesthetics by the placenta, defined by the ratio of anesthetic concentration in fetal vein and maternal artery, multiplied by fetal flow rate. Placental clearance was compared between different fetal perfusion states and anesthetics. Hypoperfusion resulted in a lower clearance of sevoflurane and isoflurane compared with control ($P = 0.002$, $P < 0.001$) and intermediate ($P = 0.04$, $P = 0.018$) perfusion. Clearances of sevoflurane and isoflurane were comparable during control perfusion ($P = 0.93$), intermediate perfusion ($P = 1.00$), and hypoperfusion ($P = 0.88$). Thus, maintenance of volatile anesthetics at a marginally low concentration may not be necessary when fetal distress is observed during emergency cesarean delivery because placental transfer of volatile anesthetics decreases with decreasing fetal perfusion.

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During cesarean section under general anesthesia, administration of a high concentration of volatile anesthetics should be avoided because of the risk of rapid drug transmission across the placenta and suppression of fetal activity [1, 2]. In particular, caution is especially required when fetal distress is observed in the setting of emergency cesarean delivery. Maintenance of general anesthesia with a low concentration of volatile anesthetics, however, places parturients at increased risk of intraoperative awareness during cesarean delivery [3, 4]. Despite the issues surrounding optimal concentrations of volatile anesthetics, clinical studies on placental transfer of volatile anesthetics under conditions of fetal hypoperfusion remain a challenge, given ethical concerns regarding the control of fetal perfusion. Accordingly, we used a dual perfused human placental cotyledon model to investigate placental clearance of volatile anesthetics at different fetal perfusion rates in parturients undergoing elective cesarean section. This model has been validated for the evaluation of placental propofol transfer [5, 6]. It allows for simultaneous measurement of the placental transfer of two volatile anesthetics and is advantageous because transfer of anesthetics across the placenta largely differs between cotyledons.

This study was approved by the institutional review board of Hyogo College of Medicine (no. 184, 527), and written informed consent was obtained from each patient. We obtained five placentas from parturients undergoing elective cesarean section. The dual perfused human placental cotyledon model was prepared according to Schneider et al. [7] and Miller et al. [8]. Briefly, we perfused the placenta using three 20-gauge cattelan needles

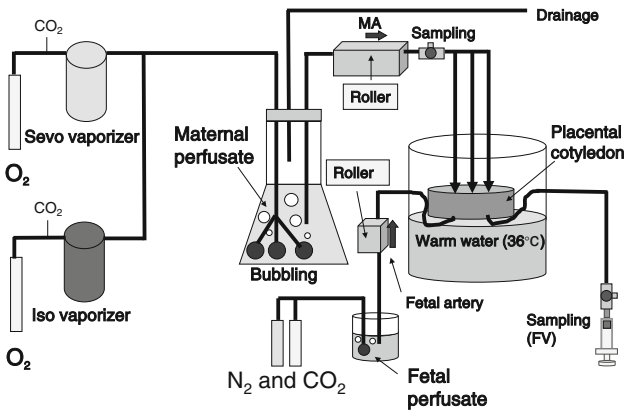

Fig. 1 Schematic representation of the experimental setup. On the maternal side, we delivered 1.5 % sevoflurane (*Sevo*) and 1.0 % isoflurane (*Iso*) in 95 % oxygen and 5 % carbon dioxide, each at the rate of 2 l/min (total, 4 l/min) through the vaporizer, and bubbled the maternal perfusate using air stones in a flask. On the fetal side, we cannulated a paired fetal artery and vein. The flow rate on the maternal side was 15 ml/min; the flow rate on the fetal side was consecutively decreased from 3, 2, to 1 ml/min. Perfusate samples were collected from the maternal artery (*MA*) and fetal vein (*FV*)

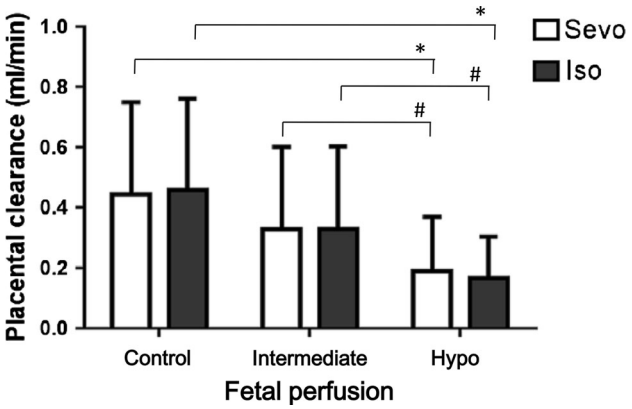

Fig. 2 Comparison of placental clearance of volatile anesthetics at three stages (control perfusion, intermediate perfusion, and hypoperfusion). Fetal flow rates were 3 ml/min for control perfusion, 2 ml/min for intermediate perfusion, and 1 ml/min for hypoperfusion. $^{*}P < 0.01$; $\#P < 0.05$. *Sevo* sevoflurane, *Iso* isoflurane, *Hypo* hypoperfusion

inserted into the maternal surface of the placenta that were likened to the three spiral arteries (Fig. 1). On the fetal side, we cannulated a paired fetal artery and vein supplying a peripheral cotyledon with a 3 Fr. feeding tube. For tissue culture, we used Medium 199 modified with Earle's salts (ICN Biomedicals, Aurora, OH, USA) containing heparin (2,500 U/l), gentamycin (50 mg/l), and glucose (1.0 g/l), as maternal and fetal perfusates [5, 6]. We delivered 1.5 % sevoflurane and 1.0 % isoflurane in 95 % oxygen and 5 % carbon dioxide at a rate of 2 l/min (total, 4 l/min) for each through the vaporizer and bubbled the maternal perfusate using air stones in a flask. The fetal perfusate was bubbled with gas containing 95 % nitrogen and 5 % carbon dioxide at 1 l/min [8].

While the maternal side of the placenta was perfused at a fixed rate of 15 ml/min, the flow rate on the fetal side was consecutively decreased from 3 ml/min (control perfusion) to 2 ml/min (intermediate perfusion), and then to 1 ml/min (hypoperfusion). A time interval of more than 10 min was introduced between each stage. Ten minutes after the start of perfusion at each rate, perfusate samples were collected from the maternal artery (MA) and fetal vein (FV) using a 10-ml glass syringe in the closed system. Concentrations of volatile anesthetics were measured by gas chromatography (GC-14B; Shimadzu, Tokyo, Japan).

All data are expressed as mean ± standard deviation. Placental transfer was assessed by the clearance of volatile anesthetics by the placenta, defined by the ratio of anesthetic concentrations in FV and MA ("F/M ratio") multiplied by fetal flow rate. Differences between and within groups after repeated measurements of placental clearance (i.e., F/M ratio) were analyzed by two-way repeated analysis of variance, with anesthetic as a factor and time points as repeated factors. The Student–Newman–Keuls test was performed for post hoc comparisons. The SigmaPlot 12 (Systat Software, Chicago, IL, USA) software package was used for statistical analyses. $P < 0.05$ was considered statistically significant.

F/M ratios for sevoflurane and isoflurane were 0.15 ± 0.10 and 0.15 ± 0.10 during control perfusion, 0.16 ± 0.14 and 0.16 ± 0.14 during intermediate perfusion, and 0.19 ± 0.18 and 0.17 ± 0.14 during hypoperfusion, respectively. There were no significant differences in F/M ratios between the two anesthetics ($P = 0.44$), or by fetal perfusion state ($P = 0.94$). Placental clearance of both sevoflurane and isoflurane during hypoperfusion was decreased to approximately 40 % of that obtained during control perfusion ($P = 0.002$, $P < 0.001$, respectively) and 55 % of that obtained during intermediate perfusion ($P = 0.04$, $P = 0.018$, respectively) (Fig. 2). Between sevoflurane and isoflurane, placental clearance was comparable during control perfusion ($P = 0.93$), intermediate perfusion ($P = 1.00$), and hypoperfusion ($P = 0.88$).

In the present study, placental clearance of sevoflurane and isoflurane at a steady state significantly decreased as the fetal flow rate was decreased. On the other hand, F/M ratios were comparable between the two volatile anesthetics at different fetal perfusion states. Our findings are consistent with a previous study, which reported that a decrease in placental propofol clearance was observed with decreasing umbilical flow rate whereas propofol concentrations in MA and FV remained uninfluenced [6]. Our results suggest that placental transfer of highly lipophilic anesthetics, including propofol and volatile anesthetics used in this study, may be limited by flow-dependent

passive diffusion rather than partitioning of volatile anesthetics into the placenta, which might explain why F/M ratios were comparable between sevoflurane and isoflurane, despite the difference in lipophilicity (fat/gas partition coefficient: 34 for sevoflurane, 64 for isoflurane) [9].

Clinical studies on placental transfer of volatile anesthetics [10–12] have been limited. Furthermore, there was no study that showed the difference of placental transfer between sevoflurane and isoflurane clearly. Thus, we tried this simultaneous administration protocol to confirm the differences between these two volatile anesthetics because we found considerable individual variation of each cotyledon from our previous experiment [13]. In the present study, F/M ratios of volatile anesthetics (0.15–0.19) were lower compared to previously reported values (0.27–0.97) [10–12]. This discrepancy may be explained, at least in part, by the single-pass model employed in the present study [13–15]. Moreover, we have to consider the differences of administration protocols with volatile anesthetics among these studies [10–12] and simultaneous administration of two volatile anesthetics. F/M ratio is a parameter for the equilibrium of anesthetic in MA and FV and thus does not provide specific information on transfer rates of anesthetics across the placenta. Yet, the present study demonstrated a significant decrease in placental clearance of volatile anesthetics with a decreased fetal flow rate, suggesting that an accumulation of volatile anesthetics in the fetus may also be reduced by decreased fetal flow. Fetal distress is associated with four contributing factors: maternal, fetal, placental, and umbilical cord factors. Our model corresponds to problems such as fetal low cardiac output and blood flow failure in the umbilical cord. The fetal flow dependence of placental transfer of volatile anesthetics in our results is advantageous for a distressed fetus.

A limitation of the present study is the large variation in placental drug transfer between each placental cotyledon model prepared, as reflected by F/M ratios of volatile anesthetics. Differences in individual vessel strike, thrombus in the vessels, intervillous space, and viability between each placenta might be responsible. Further, we cannot declare that placental transfers of sevoflurane and isoflurane in the concentrations used clinically are almost the same from the aspect of this small-sized sample. This study was completely under the condition of being not only a single-pass model but also a steady-state investigation. Therefore, we have to be more careful when we consider placental transfer of volatile anesthetics in clinical anesthesia using these results. Specifically, we did not examine the condition in which the maternal concentration of volatile anesthetic increases immediately, such as the induction of general anesthesia in cases of cesarean section. We plan that this will be our next subject for study. In addition, the blood distribution ratio of volatile anesthetics to major organs such as the brain and heart increases in the state of low fetal output, which should also be taken into account [16].

In conclusion, placental clearance of volatile anesthetics significantly decreased with a decreasing fetal flow rate in our dual perfused human placental cotyledon model. On this basis, maintaining volatile anesthetics at a marginally low concentration may not be necessary when fetal distress is observed during emergency cesarean delivery under general anesthesia. Further clinical studies to assess fetal activity are necessary to confirm our conclusion.

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Conflict of interest None to declare.

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