

## Hypocapnia Attenuates, and Nitrous Oxide Disturbs the Cerebral Oximetric Response to the Rapid Introduction of Desflurane

The aim of this study was to develop a nonlinear mixed-effects model for the increase in cerebral oximetry ( $rSO_2$ ) during the rapid introduction of desflurane, and to determine the effect of hypocapnia and  $N_2O$  on the model. Twelve American Society of Anesthesiologist physical status class 1 and 2 subjects were allocated randomly into an Air and  $N_2O$  group. After inducing anesthesia, desflurane was then increased abruptly from 4.0 to 12.0%. The  $P_{ETCO_2}$ ,  $P_{ETDESF}$  and  $rSO_2$  were recorded at 12 predetermined periods for the following 10 min. The maximum increase in  $rSO_2$  reached +24-25% during normocapnia. The increase in  $rSO_2$  could be fitted to a four parameter logistic equation as a function of the logarithm of  $P_{ETDESF}$ . Hypocapnia reduced the maximum response of  $rSO_2$ , shifted the  $EC_{50}$  to the right, and increased the slope in the Air group.  $N_2O$  shifted the  $EC_{50}$  to the right, and reduced the slope leaving the maximum  $rSO_2$  unchanged. The  $N_2O$ -effects disappeared during hypocapnia. The cerebrovascular reactivity of  $rSO_2$  to  $CO_2$  is still preserved during the rapid introduction of desflurane.  $N_2O$  slows the response of  $rSO_2$ . Hypocapnia overwhelms all the effects of  $N_2O$ .

Key Words : Cerebral Oximetry; Desflurane; Anesthesia

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## INTRODUCTION

The rapid introduction of desflurane produces sympathetic stimulation and associated changes, which are represented by increases in blood pressure, heart rate and pupil diameter (1-3). The cerebrovascular response to a rapid increase in desflurane was also reported and considered to be either a coincident or independent change from hemodynamic stimulation (4, 5). There are few reports on the cerebral oximetric response to the introduction of desflurane.

Hoffman et al. (6) observed an increase in the cerebral tissue  $PO_2$  during desflurane anesthesia, and suggested the increased  $PO_2$  to be indicative of the improved cerebral oxygenation status. The cerebral oximetry ( $rSO_2$ ) values can be compared with the focal cerebral tissue  $PO_2$ . Moreover, the increase in  $rSO_2$  can be regarded not only as an improvement in the cerebral oxygenation status but also as a resultant hyperemia. It was hypothesized that  $rSO_2$  would also respond to the rapid introduction of desflurane.

Carbon dioxide plays an important role in regulating the cerebral blood flow. Hence, hypocapnia would be favorable in desflurane-induced hyperemic changes to the brain. The addition of  $N_2O$ , which is commonly used in everyday practice of anesthesia, decreases the minimum alveolar concentration (MAC) of desflurane and would attenuate the response

of  $rSO_2$  by increasing the depth of anesthesia if the change in  $rSO_2$  is dependent on systemic sympathetic stimulation. This study examined the inherent cerebrovascular effects of  $N_2O$ . It is expected that this study will help to improve the understanding of the cerebrovascular changes during desflurane anesthesia.

Accordingly, in order to demonstrate that hypocapnia or the addition of  $N_2O$  can modify the response of  $rSO_2$ , the concentration (dose)-response relationship for the change in  $rSO_2$  during the rapid introduction of desflurane was examined using a nonlinear mixed-effects model in a grouped repeated design.

## MATERIALS AND METHODS

After obtaining institutional research board approval (2008-1-26) and written informed consent, 12 American Society of Anesthesiologist (ASA) physical status class 1-2 adults who underwent a variety of surgical procedures requiring general anesthesia were enrolled in this study. The exclusion criteria included subjects with alleged respiratory, cardiovascular, and cerebral diseases, or were taking associated medications. No premedication was given. The subjects were allocated randomly to an Air (n=6) or  $N_2O$  group (n=6).

In addition to the standard monitoring equipment, the emitter-sensor couplet of a cerebral oximeter (INVOS 5100B, Somanetics®, Troy, OH, U.S.A.) was attached to the right brow, and a sensor from a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) was attached to the appropriate finger to obtain the continuous arterial pressure, heart rate, and cardiac output. The concentrations of CO<sub>2</sub>, N<sub>2</sub>O and desflurane were measured using the airway module embedded in an anesthesia machine (S/5 Avance, Datex-Ohmeda, Helsinki, Finland). Anesthetic induction and maintenance were achieved as described by our institution's standard anesthetic guidelines. Briefly, vecuronium (0.08-0.1 mg/kg), remifentanyl (computer-estimated effect-site concentration, Ce=3.0 ng/mL) were administered intravenously as required after confirming the loss of consciousness with a titrated dose of intravenous propofol (1.5-2.0 mg/kg). Remifentanyl was administered using a target-controlled infusion device (Orchestra® Base Primea, Fresenius-Kabi, Bad Homburg, Germany). Desflurane (6.0% dial-concentration) were inhaled. After the trachea was intubated, the infusion of remifentanyl was stopped and the dial-concentration of desflurane was adjusted to 4.0%. In the Air group, medical air was added to the oxygen to ensure an inspired oxygen fraction of 0.4. N<sub>2</sub>O was added in the N<sub>2</sub>O group. Mechanical ventilation was started with V<sub>T</sub>=8 mL/kg and RR=10 breath/min while permitting an inter-subjects difference in the end-tidal concentration of CO<sub>2</sub> (PET<sub>CO2</sub>). The corresponding PET<sub>CO2</sub> was 33 ± 4 (ranged 24-41) mmHg throughout the study period. The SpO<sub>2</sub> values were approximately 98-100% during the course of the study.

After stabilization for approximately 20 min until the Ce of remifentanyl fell to below 0.3, the average end-tidal (PET<sub>DESFL</sub>) and inspired (PFI<sub>DESFL</sub>) desflurane reached 4.0%, and the dial-concentration of desflurane was increased to 12.0%, simultaneously with 6 L/min of a fresh gas flow rate and the PET<sub>DESFL</sub> converged within 90% of the PFI<sub>DESFL</sub>. This time was set to time 0 (T<sub>0</sub>).

### Measurements and calculations

The basic preanesthetic measurements included the body weight, height, rSO<sub>2</sub>, mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), body surface area (BSA), and derived cardiac index (CI). Consecutive measurements, including the rSO<sub>2</sub>, SpO<sub>2</sub>, MAP, HR, CI, PET<sub>DESFL</sub>, PFI<sub>DESFL</sub>, and PET<sub>CO2</sub> were recorded at T<sub>0</sub> and the following periods; 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 8.0, and 10 min from T<sub>0</sub>. The measurement was stopped when the MAP > 120 mmHg or < 50 mmHg, and the HR > 130 beats/min or < 45 beats/min. However, the measurements before stopping were also included in the analysis. Two subjects, one in the Air group and one in the N<sub>2</sub>O group, showed hypotension (MAP < 50 mmHg), which was treated promptly with intravenous ephedrine 5 mg. The ΔrSO<sub>2</sub> was defined as the difference between the rSO<sub>2</sub> at a given time from rSO<sub>2</sub> at T<sub>0</sub>. The estimated alveo-

lar concentration of desflurane (PET/FI<sub>DESFL</sub>) was defined and calculated as the PET<sub>DESFL</sub> divided by the final PFI<sub>DESFL</sub>.

### Reliability of the rSO<sub>2</sub> measurements

By examining the variance components using a random intercept and slope model, the reliability of the two rSO<sub>2</sub> measurements was tested before and after the induction of anesthesia. The value of rSO<sub>2</sub> was predicted from hemoglobin with a combination of the anesthesia-effect and subject-effect as random effects. The intra-class correlation ( $\rho$ ) was defined and estimated,

$$\rho = \frac{\tau^2}{\tau^2 + \sigma^2}$$

where  $\tau$  is the between-subjects variance and  $\sigma$  is the within-subjects variance. The variance of the between-subjects random effects was composed of the variance of each random effect, in this case,  $\tau^2 = \tau_{\text{intercept}}^2 + \tau_{\text{slope}}^2$ . Interpretation of  $\rho$  was descriptive. A high  $\rho$  (>0.90) suggests that the between-subjects component was dominant in the total variances, which also indicated a good reliability of the repeated measurement within-subjects.

### Hemodynamic variables

The temporal changes in the MAP, HR, and CI were analyzed by an analysis of the covariance (ANCOVA). The ANCOVA model was fitted as a function of time, and N<sub>2</sub>O was used as a grouping variable. When the N<sub>2</sub>O-effect was significant, 12 pairwise comparisons were made at each time period using the adjusted *P* according to the Dunn-Sidak procedures ( $P' = 1 - [1 - P]^{12}$ ).

### Modeling for temporal changes in PET/FI<sub>DESFL</sub>

The temporal change in the PET/FI<sub>DESFL</sub> was modeled using an exponential function of time as follows:

$$\text{Predicted PET/FI}_{\text{DESFL}} = f(\text{time}) = \text{Asym} + (y_0 - \text{Asym}) \times e^{-\text{lrc} \times \text{time}}$$

where Asym is the asymptote as time approaches infinity, and  $y_0$  is PET/FI<sub>DESFL</sub> at T<sub>0</sub>. The parameter, lrc, is the logarithm of the rate constant, ensuring a positive rate constant. The time to half ( $t_{0.5}$ ) can be derived from  $\log(2)/\text{lrc}$ . The parameter time is the elapsed time from T<sub>0</sub>. PET/FI<sub>DESFL</sub> was fitted as a function of time, where the covariates, such as N<sub>2</sub>O, PET<sub>CO2</sub>, MAP, HR, and CI, were analyzed to demonstrate their effects on the individual parameters; Asym,  $y_0$ , and lrc. The term for the random effects was constructed initially with the intercepts of Asym,  $y_0$ , and lrc. Between the random effects, the high correlations ( $r > 0.9$ ) were removed by under-parameterization. The variance component of the random effects belonging to the subjects was also examined.

### Modeling for the increase in $\Delta rSO_2$ for $PET_{DESf}$

The  $\Delta rSO_2$  increased as a function of the logarithm of  $PET_{DESf}$  according to the following equation:

$$\Delta rSO_2 = f[\log(PET_{DESf})] = R_{max} + \frac{R_0 - R_{max}}{1 + e^{[\log(PET_{DESf}) - LC_{50}]/\theta}}$$

where  $R_{max}$  is the maximum response,  $R_0$  is the initial response,  $LC_{50}$  is the  $\log(PET_{DESf})$  value at the inflection point [=  $\log(EC_{50})$ ], and  $\theta$  is simply the inverse slope factor. This is known as the four-parameter logistic model, which relates the response of  $\Delta rSO_2$  to an input  $PET_{DESf}$  using a sigmoidal function. When describing and discussing the results, all the  $LC_{50}$  was translated in terms of the  $EC_{50}$ ,  $e^{LC_{50}}$ .

The effects of  $PET_{CO_2}$  and  $N_2O$  on the individual model parameters,  $R_{max}$ ,  $R_0$ ,  $LC_{50}$ , and  $\theta$ , were the primary focus of this study. The other covariates, MAP, HR and CI, were also examined using the stepwise including and excluding technique. The term for the random effects was constructed with the intercepts of  $R_{max}$  and  $\theta$ . No random effects of  $R_0$  or  $LC_{50}$  were assumed. The block diagonal matrix was specified to represent the random effects variance-covariance matrix. The heteroscedasticity of the within-subject errors, particularly at low  $PET_{DESf}$  levels, was accommodated using a variance function, which is a power of the absolute value of the variance covariate.

The final model was chosen based on a log-likelihood test and an analysis of variance of nonlinear mixed-effects model. The median (Q1-Q3) standardized residuals were calculated to determine the quality of the prediction for the population. The typical values of the overall cerebrovascular reactivity of  $rSO_2$  to  $CO_2$  were estimated from ( $R_{max(40 \text{ mmHg})} - R_{max(30 \text{ mmHg})}$ )/

**Table 1.** Summary statistics for the basic measurements and calculations

Parameters	Overall (n=12)	Air group (n=6)	N <sub>2</sub> O group (n=6)
Age (yr)	42 ± 10	45 ± 6	39 ± 12
Sex (male/female)	6/6	3/3	3/3
Body weight (kg)	63 ± 10	64 ± 12	62 ± 9
Height (cm)	162 ± 9	160 ± 10	164 ± 9
BSA (m <sup>2</sup> )	1.67 ± 0.17	1.67 ± 0.19	1.67 ± 0.17
Hemoglobin (g/dL)	13.8 ± 1.2	13.6 ± 1.2	14.0 ± 1.2
MAP (mmHg)	94 ± 15	90 ± 6	99 ± 20
HR (beat/min)	71 ± 12	62 ± 10	71 ± 12
CO (L/min)	5.80 ± 1.67	6.50 ± 1.86	5.10 ± 1.23
CI (L/min/m <sup>2</sup> )	3.48 ± 0.95	3.93 ± 1.07	3.03 ± 0.59

Values are reported as the mean ± SD.

All measurements in the Table 1 show no significant differences between the two groups ( $P \geq 0.05$ ).

BSA, body surface area, estimated by  $71.84 \times \text{Body Weight}^{0.425} \times \text{Height}^{0.725} / 10,000$ ; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index.

10 mmHg in each group.

Unless specified otherwise, all values are reported as mean ± SD. All statistical analyses, including nonlinear mixed-effects modeling, inferential statistics, and arithmetic calculations, were performed using S-Plus 8.0 (Insightful Corp., Seattle, WA, U.S.A.), which was enhanced using the nlme (nonlinear mixed effects) version 3.3.2 library (Pinheiro and Bates, U.S.A.). Therefore, estimates of the parameters for the fixed effects of the mixed-effects model are presented as the mean (standard error of the mean), and the residuals of the fitted model were presented as the median (Q2-Q3). Random effects were presented as overall SD of the random effects. Between the groups, the basic measurements and calculations were compared using a Wilcoxon rank test, and the gender distribution was compared using a Fisher's exact test. A multiple Wilcoxon rank test was used with the  $P'$  to compare the pairwise contrasts for the groups at 12 periods.  $P$  values < 0.05 were considered significant.

## RESULTS

### Measurements, calculations, and the reliability of the measurements

There was no significant difference in the basic measurements between the groups (Table 1). There was also no sig-

**Table 2.** Summary statistics for the repeated measurements during rapid introduction of desflurane

Parameters	Overall (n=138)	Air group (n=67)	N <sub>2</sub> O group (n=71)
MAP (mmHg)	74 ± 18 (44-123)	72 ± 20	76 ± 15
HR (beat/min)	81 ± 22 (45-150)	74 ± 16	87 ± 25
CO (L/min)	6.32 ± 2.01 (2.00-11.90)	6.02 ± 1.62	6.61 ± 2.29
CI (L/min/m <sup>2</sup> )	3.82 ± 1.32 (1.35-7.83)	3.64 ± 1.03	4.00 ± 1.54
$PET_{CO_2}$ (mmHg)	33 ± 4 (24-41)	33 ± 3	34 ± 4
SpO <sub>2</sub> (%)	99 ± 1 (98-100)	98 ± 1	99 ± 1
$PET_{N_2O}$ (%)	-	-	52 ± 4
$PFI_{N_2O}$ (%)	-	-	53 ± 4
$PET_{DESf}$ (%)	8.9 ± 1.9	9.0 ± 2.0	8.9 ± 1.8
Final $PFI_{DESf}$ (%)	11.5 ± 0.7	11.9 ± 0.9	11.1 ± 0.3

Values are reported as the mean ± SD (min-max).

Measurements of  $PET_{CO_2}$ , SpO<sub>2</sub>, and final  $PFI_{DESf}$  in the Table 2 show no significant difference between the two groups ( $P \geq 0.05$ ).

The values of MAP, HR, CO, CI, and  $PET_{DESf}$  were not compared based on the simple mean ± SD, which is meaningless.

n, number of total repeated measurements for 6 subjects in each group; BSA, body surface area; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index;  $PET_{CO_2}$ , end-tidal CO<sub>2</sub> concentration; SpO<sub>2</sub>, pulse oximetry;  $PET_{N_2O}$ , end-tidal N<sub>2</sub>O concentration;  $PFI_{N_2O}$ , inspired N<sub>2</sub>O concentration;  $PET_{DESf}$ , end-tidal desflurane concentration; Final  $PFI_{DESf}$ , final inspired desflurane concentration.

nificant difference in the repeated measurements during rapid introduction of desflurane between the groups (Table 2). The mean rSO<sub>2</sub> values before and after anesthesia were 68 ± 8%, whose anesthesia-effect was estimated to be +0.4% but failed

to reach significance at the 5% level ( $P=0.127$ ). The  $\rho$ , estimated intra-class correlation between the two rSO<sub>2</sub> measurements was 0.9336, indicating that the repeated measurements of rSO<sub>2</sub> were reliable within-subjects.

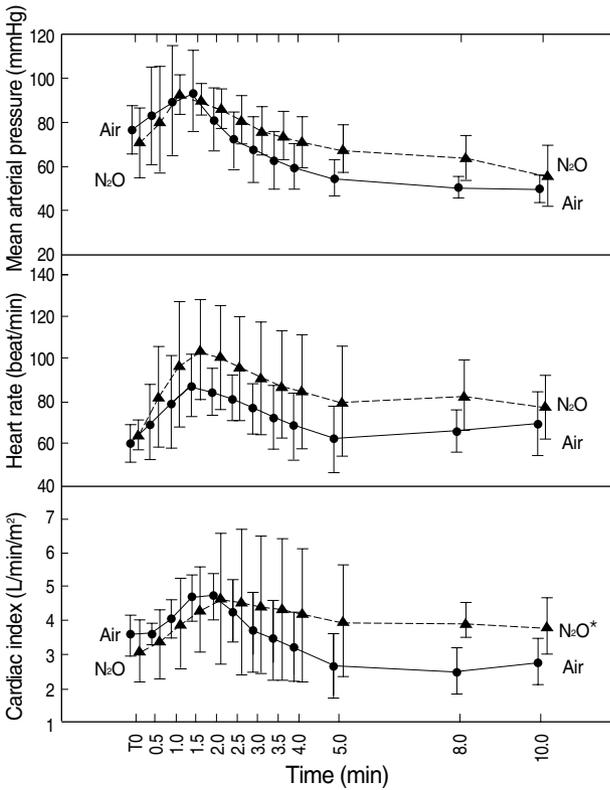


Fig. 1. Temporal changes in the MAP (upper panel), HR (middle panel) and CI (lower panel). During rapid introduction of desflurane, MAP, HR, and CI show consistent initial increase (near 30%, 1.5 min) and a subsequent decrease. N<sub>2</sub>O does not blunt these increases, and modifies the temporal pattern of the change in CI significantly\* ( $P=0.021$ ) regardless of there being no significant difference at any time period by multiple comparisons ( $P' \geq 0.05$ ).

Hemodynamic variables

The MAP, HR and CI evenly showed an initial increase with a subsequent decrease (Fig. 1). The temporal changes in the MAP, HR, and CI were statistically significant ( $P < 0.001$ ,  $P=0.007$ , and  $P=0.001$ , respectively). N<sub>2</sub>O significantly affected the pattern of the temporal changes in the CI ( $P=0.021$ ) but not MAP ( $P=0.059$ ) or HR ( $P=0.877$ ). Changes in N<sub>2</sub>O had no significant effect on the CI at any separate time period ( $P' \geq 0.05$  between groups). Despite the statistical insignificance, N<sub>2</sub>O mildly augmented the increase in the HR (+17 beats/min), and reduced the slope of the decrease in the HR, MAP, and CI.

Modeling for the temporal changes in PET/F<sub>I</sub>DES<sub>F</sub>

The temporal changes in PET/F<sub>I</sub>DES<sub>F</sub> were modeled by

$$\text{Predicted PET/F}_{I\text{DES}_F} = f(\text{time}) = 0.9080 + (0.6196 - 0.9080) \times e^{-e^{-0.7836 \times \text{Time}}}$$

when PET<sub>CO<sub>2</sub></sub>=40 mmHg and CI=3.8 L/min/m<sup>2</sup> (Fig. 2). The time to half ( $t_{0.5}$ ) was estimated to be approximately 1.5 min from T<sub>0</sub>. In concordance with the well-known concept on the pharmacokinetics of volatile anesthetics, the PET<sub>CO<sub>2</sub></sub> ( $P=0.001$ ) and CI ( $P < 0.001$ ) significantly modified the Asym, not lrc or y<sub>0</sub>. A decrease in PET<sub>CO<sub>2</sub></sub> increased the Asym by 0.0014 (0.0009, SE)/mmHg and increase the CI by 0.0081 (0.0019, SE)/L/min/m<sup>2</sup>. No other covariates, such as the N<sub>2</sub>O, MAP, or HR, modified the parameters. There was a strong correlation between the random effects for the intercepts of

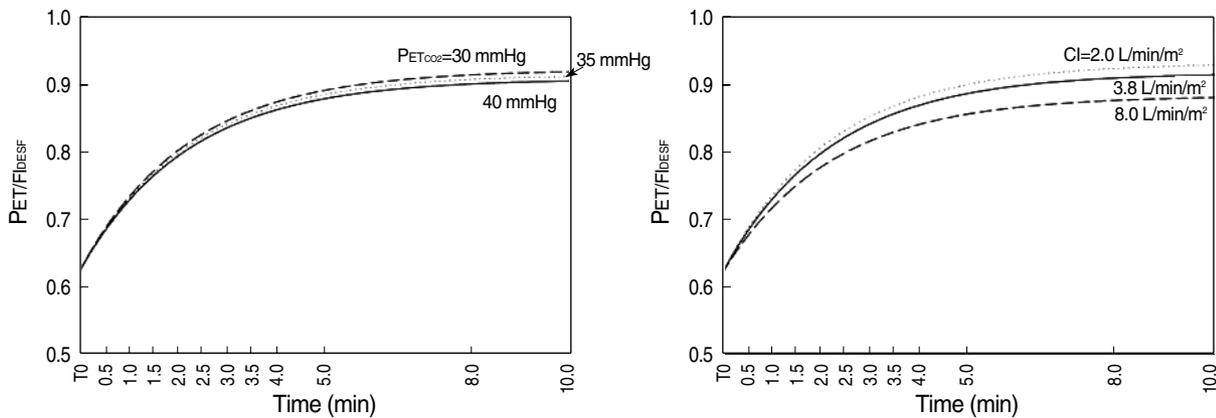


Fig. 2. Predicted temporal changes in the PET/F<sub>I</sub>DES<sub>F</sub> for variables PET<sub>CO<sub>2</sub></sub> (left panel), and CI (right panel). Typical curves were redrawn separately for the changes in PET<sub>CO<sub>2</sub></sub> and CI within the reasonable range of the data. The time to half ( $t_{0.5}$ ) was estimated to be approximately 1.5 min. PET/F<sub>I</sub>DES<sub>F</sub>=estimated alveolar concentration of desflurane; PET<sub>CO<sub>2</sub></sub>=end-tidal carbon dioxide concentration (mmHg); CI, cardiac index (L/min/m<sup>2</sup>).

Asym and  $y_0$  ( $r=0.983$ ) and random effects for  $y_0$  were removed. Random effects were  $\pm 0.0458$ . The standardized residuals were normally distributed,  $-0.1803$  ( $-0.7387$ - $0.5468$ ).

### Modeling for the increase in $\Delta rSO_2$ for $PET_{DESf}$

The final model for the increase in  $\Delta rSO_2$  were determined using the following equation

$$\text{Predicted } \Delta rSO_2 = f[\log(PET_{DESf})] \\ = 25.9425 + \frac{-0.3362 - 25.9425}{1 + e^{[\log(PET_{DESf} - 40) - 9.3549]/0.1084}}$$

where  $PET_{CO_2} = 40$  mmHg in the Air group. In the model,

**Table 3.** Parameter estimates of the model to fit  $\Delta rSO_2$  according to  $PET_{CO_2}$

Groups	$R_{max}$ (%)	$EC_{50}$ (%)	$\theta$
Air group (n=6)			
$PET_{CO_2} = 40$ mmHg	25.9425 (4.6705)	9.3549 (1.0516)	0.1084 (0.0252)
$PET_{CO_2} = 30$ mmHg	10.5571 (1.7997)*	9.4348 (1.0359)*	0.0276 (0.0083)*
N <sub>2</sub> O group (n=6)			
$PET_{CO_2} = 40$ mmHg	24.8791 (4.6705)	10.0976 (1.0070) <sup>†</sup>	0.1851 (0.0245) <sup>†</sup>
$PET_{CO_2} = 30$ mmHg	11.9812 (1.7997)*	9.4565 (0.0359)*	0.0276 (0.0083)*

Values are reported as the mean (standard error of mean).

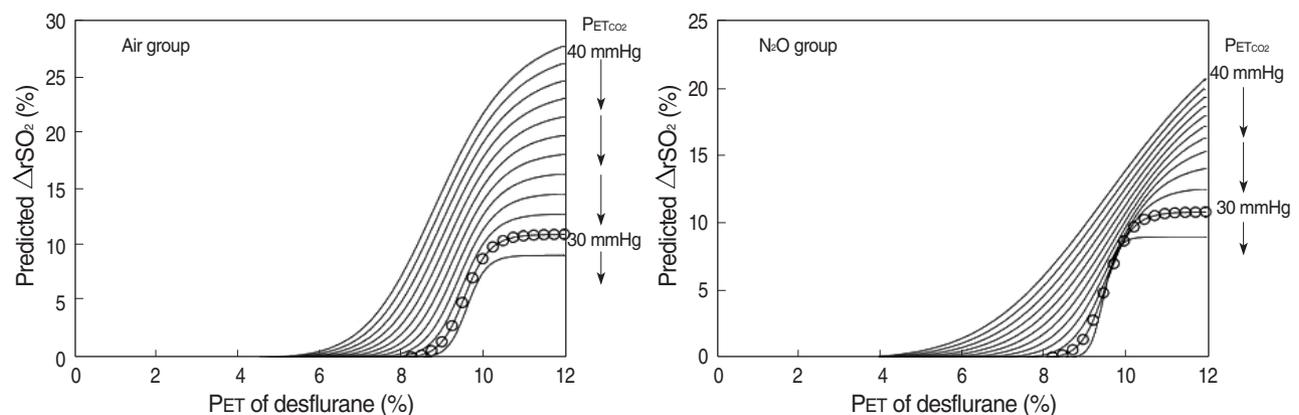
$R_{max}$ , the destined maximum response of  $rSO_2$ ;  $EC_{50}$ , median effective concentration of desflurane,  $e^{LC_{50}}$ ;  $\theta$ , the inverse slope factor;  $PET_{CO_2}$ , end-tidal concentration of carbon dioxide.

The \* mark denotes the statistically significant difference from  $PET_{CO_2} = 40$  mmHg ( $P < 0.001$ ); The <sup>†</sup> mark denotes the statistically significant difference from Air group ( $P < 0.001$ ).

$R_0$  was constant at  $-0.3362$  ( $0.2894$ ) and  $R_{max}$ ,  $EC_{50}$  and  $\theta$  were modified by a combination of  $PET_{CO_2}$  and  $N_2O$  (Table 3). No other covariates, such as MAP, HR, or CI, had a significant effect on the parameters ( $P \geq 0.05$ ). The effects of  $CO_2$  on  $R_{max}$  and  $\theta$  were estimated within the course of the increase in  $PET_{DESf}$  (Fig. 3). However, the typical values for the cerebrovascular reactivity to  $CO_2$  could be estimated by  $1.5389\%/mmHg$  in the Air group, and  $1.2898\%/mmHg$  in the  $N_2O$  group ( $P \geq 0.05$  between groups). Random effects were  $\pm 2.3872$ . The standardized residuals were normally distributed,  $0.1798$  ( $-0.4629$ - $0.4713$ ).

## DISCUSSION

During the rapid introduction of desflurane, the curve for the temporal increase in  $PET/FI_{DESf}$  from a concentration of 4% to 12% in this study agreed reasonably well with a textbook example regarding the effect of  $PET_{CO_2}$  and CI. High residuals are indicative of low predictability and the need of the two-exponential curves. We did not attempt to refine the model because it was beyond the interest of the present study. Prefilled  $N_2O$  in the lung had no effect on the curve. The rapid introduction of desflurane produced a similar hemodynamic stimulatory effects to previous reports. Stimulation peaked at approximately 1.5 min from T0, which approximated to  $t_{0.5}$  of the curve for the increase in  $PET/FI_{DESf}$ .  $N_2O$  failed to block the stimulation of MAP and HR, or mildly promoted the increased pattern, which is comparable to the  $N_2O$ -induced changes in pupil diameter reported by Daniel et al. (3). As expected,  $rSO_2$  also increased up to 24-25% according to the increase in  $PET_{DESf}$  in a concentration-dependent manner. The residuals were extremely small and independent of any possible violation by the MAP, HR, or CI. This study did not examine the random effects in detail. The



**Fig. 3.** Predicted  $\Delta rSO_2$  for the increase in  $PET/FI_{DESf}$  according to the change in  $PET_{CO_2}$ . The predicted  $\Delta rSO_2$  increases with increasing  $PET_{DESf}$  as a four-parameter logistic curve. At  $PET_{CO_2} = 40$  mmHg, the addition of  $N_2O$  decreases the slope of the increase, but the same maximum  $rSO_2$  lies outside of this graph. In  $N_2O$  group, both the inverse slope factor and maximum  $rSO_2$  decrease significantly with decreasing  $PET_{CO_2}$ . The  $N_2O$ -effects decrease with decreasing  $PET_{CO_2}$ , and the differences between the groups disappear when  $PET_{CO_2} = 30$  mmHg.  $PET_{DESf}$ , end-tidal concentration of desflurane (%);  $PET_{CO_2}$ , end-tidal carbon dioxide concentration (mmHg).

random effects were confined to refining the relationship between the predictors and the response by eliminating the individual variability. Modeling for the population was beyond the scope of this study. The fitted equation included three major parameters,  $R_{max}$ ,  $EC_{50}$ , and  $\theta$ .

Hypocapnia reduced the  $R_{max}$ , and increased the slope in the Air group.  $EC_{50}$  was shifted to the right slightly but significantly. This suggests that the cerebrovascular reactivity to  $CO_2$  still subsists at more than 1.5 MAC desflurane. The  $CO_2$  reactivity was not measured while the patient was awake. Therefore, the absolute values for the reactivity cannot be used to draw any real conclusion as to whether it was intact or preserved. There are no reports on the reactivity to  $CO_2$  measured at high concentrations of desflurane that could be used to compare with the present study. With 0.5-1.0 MAC desflurane, the reactivity to  $CO_2$  is considered to be preserved (7-9). In a study of 1.5 age-adjusted MAC desflurane-anesthetized children, the reactivity to  $CO_2$  was impaired (8). The estimate of the overall reactivity to  $CO_2$  of  $rSO_2$  was 1.2898-1.5389%/mmHg, which is similar to the  $1.1 \pm 0.67\%$ /mmHg estimated results from 5% desflurane-anesthetized adults by Lee et al. (9). In this study, the reactivity to  $CO_2$  was estimated during the dynamic phase of the increasing concentration of desflurane, which is unlike the steady state used by others. Its importance is unknown and so any comparison might be invalid.

Although there is some discrepancy in the measurements or design, it can be generally summarized that the cerebrovascular effect of the solitary or additional  $N_2O$  to volatile anesthetics causes an elevation (10-12), or at least no decrease (13-16) in the cerebral blood flow. Interpreting the effect of  $N_2O$  on these parameters is quite complicated. During normocapnia, the addition of 60%  $N_2O$  obviously increased the inverse slope factor  $\theta$  and shifted  $EC_{50}$  to the right in order to reduce the change in  $rSO_2$  caused by an increase in desflurane concentration, while the  $R_{max}$  was unchanged. These  $N_2O$ -effects disappeared in hypocapnia. Lowering  $PET_{CO_2}$  shifted the  $EC_{50}$  to the left and reduced the  $\theta$ s. Summary of the hypocapnia-effect in the  $N_2O$  group is the right-shift and steepening of the curve. There may be two explanations for this observation. The rapid introduction of desflurane could cause a pronounced hyperemic condition of the brain, in which no more hyperemia could be reached even by adding  $N_2O$ . The slower response in the  $N_2O$  group might indicate a disturbance of the cerebral vasculatures to changes in the desflurane concentration. The other explanation is that hypocapnia overwhelms the effect of  $N_2O$ .

The former explanation partly agrees with some previous studies that reported a cerebrovascular effect in anesthesia with a combination of  $N_2O$  and volatile anesthetics, in which  $N_2O$  had no additional effect on the volatile-induced change in cerebral blood flow velocity (16). Contradiction was also found. For example,  $N_2O$  disturbs the flow/metabolism coupling when added to sevoflurane (12). No other report has estimated the additional  $N_2O$ -effect even with a desflurane

concentration of >1.5 MAC or with a variety of  $CO_2$  tension.

The latter explanation remains to be demonstrated. There are no reports of interactions between hypocapnia and  $N_2O$ . Local factors of the brain should also be considered.  $N_2O$  or volatile anesthetics redistribute rCBF (13, 17, 18). The  $rSO_2$  measurements were limited to the frontal pole of the brain, which represent neither the global CBF nor typical rCBF.

One limitation of this study is that the protocol included 3 ng/mL Ce of remifentanyl during induction of anesthesia. It was clinically relevant to suppress the hemodynamic response due to laryngoscopy. By waiting 20 min from the discontinuation of the remifentanyl infusion, it was confirmed the Ce fell below 0.3 ng/mL. This is the minimum concentration where no hemodynamic interaction between remifentanyl and desflurane would be expected. Moreover, our episodic finding suggested that desflurane-induced sympathetic stimulation is unlikely repeat once it was stimulated, which was also inferred from the classical report by Weiskopf et al. (19).

Another shortcoming of this study is the well-known limitations of  $rSO_2$ . It is believed that the confounders had been eliminated. The hemoglobin concentrations and  $PET_{CO_2}$  values were similar in both groups, which would be regarded a major determinant for the change in  $rSO_2$ . The  $SpO_2$  values were all within 98-100%, and the MAP values were within 44-123 mmHg. Only two subjects showed a MAP <50 mmHg. The within-subject variability was confirmed to be <10% with the reliability test using the intra-class correlation. The value of the intra-class correlation in examining the reliability of the repeated medical data was well described by Everitt and Rabe-Hesketh (20). The inter-subjects variability of  $rSO_2$  was also removed by considering the difference from the baseline. There was a relatively small number of subjects enrolled in this study. However, the nature of mixed-effects modeling can overcome the size of the sample. The limitations related to the small sample size always arise from the inevitable inter-individual variability, which can be eliminated by mixed-effects modeling. The quality of our fitted model was exceptionally good, and the results and conclusions are strong.

In conclusion, a nonlinear mixed-effects model, which strongly predicted the response of  $rSO_2$  as the function of logarithm concentration of  $PET_{DESFL}$ , was modified only by  $PET_{CO_2}$  and  $N_2O$ . Hypocapnia shifted the response curve to the right and reduced the maximum response of  $rSO_2$  in the Air group. The cerebrovascular reactivity to  $CO_2$  still preserved within the scope of this study. It is difficult to interpret the effects of  $N_2O$  on the response of  $rSO_2$  to the rapid introduction of desflurane. There are little or no  $N_2O$ -induced hemodynamic changes and the effects of  $N_2O$  are definitely due to its inherent cerebrovascular effect.

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