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# Respiratory Sites of Action of Propofol

## Absence of Depression of Peripheral Chemoreflex Loop by Low-dose Propofol

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*Background:* Propofol has a depressant effect on metabolic ventilatory control, causing depression of the ventilatory response to acute isocapnic hypoxia, a response mediated *via* the peripheral chemoreflex loop. In this study, the authors examined the effect of sedative concentrations of propofol on the dynamic ventilatory response to carbon dioxide to obtain information about the respiratory sites of action of propofol.

*Methods:* In 10 healthy volunteers, the end-tidal carbon dioxide concentration was varied according to a multifrequency binary sequence that involved 13 steps into and 13 steps out of hypercapnia (total duration, 1,408 s). In each subject, two control studies, two studies at a plasma target propofol concentration of 0.75 $\mu$g/ml ($P_{low}$), and two studies at a target propofol concentration of 1.5 $\mu$g/ml ($P_{high}$) were performed. The ventilatory responses were separated into a fast peripheral component and a slow central component, characterized by a time constant, carbon dioxide sensitivity, and apneic threshold. Values are mean ± SD.

*Results:* Plasma propofol concentrations were approximately 0.5 $\mu$g/ml for $P_{low}$ and approximately 1.3 mg/ml for $P_{high}$. Propofol reduced the central carbon dioxide sensitivity from 1.5 ± 0.4 to 1.2 ± 0.3 ($P_{low}$; $P < 0.01$ *vs.* control) and 0.9 ± 0.1 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P_{high}$; $P < 0.001$ *vs.* control). The peripheral carbon dioxide sensitivity remained unaffected by propofol (control, 0.5 ± 0.3; $P_{low}$, 0.5 ± 0.2; $P_{high}$, 0.5 ± 0.2 $l \cdot min^{-1} \cdot mmHg^{-1}$). The apneic threshold was reduced from 36.3 ± 2.7 (control) to 35.0 ± 2.1 ($P_{low}$; $P < 0.01$ *vs.* control) and to 34.6 ± 1.9 mmHg ($P_{high}$; $P < 0.01$ *vs.* control).

*Conclusions:* Sedative concentrations of propofol have an important effect on the control of breathing, showing depression of the ventilatory response to hypercapnia. The depression is attributed to an exclusive effect within the central chemoreflex loop at the central chemoreceptors. In contrast to low-dose inhalational anesthetics, the peripheral chemoreflex loop, when stimulated with carbon dioxide, remains unaffected by propofol.

PROPOFOL is frequently used as a monoanesthetic–sedative for various diagnostic or small surgical procedures in patients who breathe spontaneously or is combined with regional anesthesia techniques for larger surgical procedures. Therefore, knowledge of the ventilatory effects of this agent is of importance. Although it is known that propofol has a depressant effect on metabolic ventilatory control, reducing the ventilatory response to hypoxia[1,2] and causing hypercapnia and sometimes even apnea,[3] the site of action of propofol within the ventilatory control system remains unknown. Propofol may affect breathing at peripheral sites (*e.g.*, peripheral chemoreceptors, lung, diaphragm), at central sites (*e.g.*, central chemoreceptors, respiratory centers), or at both sites. All halogenated volatile anesthetics, already at subanesthetic concentrations (0.05–0.2 minimum alveolar concentration [MAC]; Bispectral Index values ~70–80), cause a selective depression of oxygen ($O_2$) and carbon dioxide ($CO_2$) responses mediated by the peripheral chemoreceptors (selective with regard to responses mediated by the central chemoreceptors, which remain unaffected).[4-8] In this study, we investigated whether propofol has effects on the peripheral $CO_2$ response similar to those of the inhalational anesthetics. We studied the influence of two concentrations of propofol on the dynamic ventilatory response to hypercapnia in healthy volunteers. Using the dynamic end-tidal $CO_2$ forcing technique, the ventilatory responses were separated into a fast component originating at the peripheral chemoreceptors and a slow component at the central chemoreceptors.[9,10] Note that hypoxic studies are unable to resolve the issue of effect-site of a certain agent—anesthetic or analgesic—within the ventilatory control system. The dynamic end-tidal $CO_2$ forcing technique is especially developed to quantify the contributions of the peripheral and central chemoreflex loops to inspired minute ventilation ($\dot{V}_i$) in a noninvasive fashion and has been validated extensively in cats and humans.[9-11]

We made two important adaptations in comparison with our earlier studies on the influences of anesthetics and opioids on the dynamic ventilatory response to carbon dioxide. First, to cause a more potent stimulus to the peripheral chemoreceptors, we performed experiments at the background of moderate hypoxia (oxygen saturation, 85–90%).[10] Second, to increase the precision of the estimation of parameters related to the peripheral chemoreflex loop, we used a multifrequency binary sequence (MFBS) in end-tidal partial pressure of carbon dioxide ($P_{ET_{CO_2}}$) input involving 13 steps into and 13 steps out of hypercapnia.[12]

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## Methods

Ten healthy volunteers aged 18–25 yr (7 men and 3 women) participated in the protocols after approval was obtained from the local Human Ethics Committee (Leiden, The Netherlands). The subjects were healthy and did not have a history of tobacco or illicit drug abuse.

After arrival at the laboratory, two intravenous catheters were inserted in the left and right cubital veins (one for propofol administration and one for blood sampling). Subsequently, electrodes for electroencephalographic measurement (BisSensor; Aspect Medical Systems, Newton, MA) were placed on the head as specified by the manufacturer, and the subjects rested for 20–30 min. The subjects breathed through a face mask (Vital Signs, Totowa, NJ). Gas flows were measured with a pneumotachograph connected to a pressure transducer and were electronically integrated to yield a volume signal. Corrections were made for the changes in gas viscosity caused by changes in oxygen concentration of the inhaled gas mixtures. The inspired gas mixture was set *via* a system of mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands), which received control signals from a personal computer. This allows the forcing of end-tidal partial pressure of oxygen ($PET_{O_2}$) and $PET_{CO_2}$ according to a specified pattern in time, independent of the ventilatory response. Inspired and expired $O_2$ and $CO_2$ concentrations and arterial hemoglobin–$O_2$ saturation ($Sp_{O_2}$) were measured with a Datex Multicap gas monitor (near the mouth) and Datex Satellite Plus pulse oximeter, respectively (Datex-Engstrom, Helsinki, Finland). $PET_{O_2}$, $PET_{CO_2}$, tidal volume, respiratory frequency, $\dot{V}_i$, and $Sp_{O_2}$ were collected and stored on disc for further analysis.

The electroencephalogram was recorded using an Aspect A-2000 EEG monitor (Aspect Medical Systems; software version 3.3). The BIS values were averaged over 1-min intervals.

### Study Design

End-tidal partial pressure of carbon dioxide was varied according to an MFBS that involved 13 steps into and 13 steps out of fixed $PET_{CO_2}$ levels (low and high $CO_2$: 2 mmHg and 12 mmHg above the subjects' normal air breathing values for $PET_{CO_2}$), altogether lasting 1,408 s (23 min 28 s). Figure 1 shows a schematic diagram of the $PET_{CO_2}$ input function. The MFBS experiments were performed at a background of moderate hypoxia ($PET_{O_2}$ = 70 mmHg) and started 20 min after the initiation of hypoxia. This was done to allow time for hypoxic ventilatory decline to develop before investigating the response to $CO_2$.

### Drug Administration and Sampling

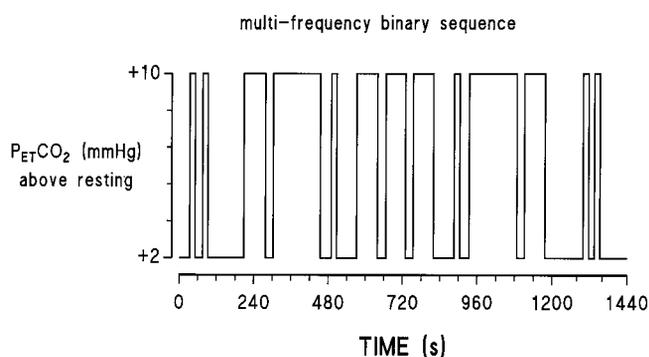A Psion palm-top computer (London, England) programmed with a three-compartment propofol pharma-



Fig. 1. The end-tidal partial pressure of carbon dioxide ($PET_{CO_2}$) multifrequency binary sequence. The y-axis represents the increase in $PET_{CO_2}$ above the individual subjects' resting $PET_{CO_2}$ values.

cokinetic data set was used to control a Becton Dickinson infusion pump (St. Etienne, France) for intravenous administration of propofol.[13] Each subject performed two control MFBS experiments, two during low-dose propofol infusion ($P_{low}$; target plasma concentration, 0.75 $\mu$g/ml) and two during high-dose propofol infusion ($P_{high}$; target plasma concentration, 1.5 $\mu$g/ml). Control studies preceded propofol studies, and low-dose propofol experiments preceded high-dose propofol experiments. MFBS studies started 15 min after plasma target concentrations had been reached. The duration of propofol infusion was 150 min (75 min for $P_{low}$ and 75 min for $P_{high}$).

Six venous propofol samples were obtained before and after each of the MFBS experiments. The samples were collected in syringes containing potassium oxalate, and propofol concentrations were determined by reverse-phase high-performance liquid chromatography.

### Data Analysis

The data were analyzed by fitting the breath-to-breath ventilatory responses to a two-compartment model, as described previously.[9–11,14] The steady-state relation of $\dot{V}_i$ to $PET_{CO_2}$ at constant $PET_{O_2}$ in humans is described by:

$$\dot{V}_i = (G_P + G_C)\,[PET_{CO_2} - B] \qquad (1)$$

where $G_P$ = the carbon dioxide sensitivity of the peripheral chemoreflex loop, $G_C$ = the carbon dioxide sensitivity of the central chemoreflex loop, and B = the apneic threshold or extrapolated $PET_{CO_2}$ of the steady-state ventilatory response to carbon dioxide at 0 $\dot{V}_i$. The sum of $G_P$ and $G_C$ is the total carbon dioxide sensitivity ($G_{TOT}$). To describe the delay in effect and dynamics of the peripheral and central ventilatory responses to $CO_2$, time delays (T) and time constants ($\tau$) are incorporated in the model. The deterministic model parameters are as follows: B; $G_C$; $G_P$; time constant of the peripheral chemoreflex loop ($\tau_P$); time constant of on-response of the central chemoreflex loop, *i.e.*, at high $PET_{CO_2}$ ($\tau_{ON}$); time constant of the off-response of the central chemoreflex

**Table 1. Estimated Model Parameters, Propofol Concentrations, and Bispectral Index (BIS) Values**

| | Control | Low-dose Propofol | ANOVA* versus Control | High-dose Propofol | ANOVA* versus Control |
|---|---|---|---|---|---|
| B (mmHg) | $36.3 \pm 2.7$ | $35.0 \pm 2.1$ | 0.009 | $34.6 \pm 1.9$ | 0.002 |
| $G_C$ ($l \cdot min^{-1} \cdot mmHg^{-1}$) | $1.53 \pm 0.36$ | $1.20 \pm 0.29$ | 0.009 | $0.92 \pm 0.12$ | < 0.001 |
| $G_P$ ($l \cdot min^{-1} \cdot mmHg^{-1}$) | $0.53 \pm 0.26$ | $0.47 \pm 0.19$ | NS | $0.46 \pm 0.19$ | NS |
| $G_{TOT}$ ($l \cdot min^{-1} \cdot mmHg^{-1}$) | $2.07 \pm 0.50$ | $1.67 \pm 0.43$ | 0.006 | $1.42 \pm 0.60$ | < 0.001 |
| $G_P/G_{TOT}$ | $0.26 \pm 0.08$ | $0.28 \pm 0.06$ | NS | $0.33 \pm 0.06$ | NS |
| Trend ($ml \cdot min^{-1} \cdot min^{-1}$) | $110 \pm 66$ | $39 \pm 61$ | NS | $20 \pm 70$ | 0.02 |
| $C_{propofol}$ A ($\mu g/ml$) | — | $0.44 \pm 0.13$ | — | $1.18 \pm 0.30$ | — |
| 95% CI | — | 0.32–0.53 | | 0.95–1.41 | |
| $C_{propofol}$ B ($\mu g/ml$) | — | $0.54 \pm 0.12$ | — | $1.27 \pm 0.32$ | — |
| 95% CI | — | 0.45–0.64 | | 0.97–1.57 | |
| $C_{propofol}$ C ($\mu g/ml$) | — | $0.49 \pm 0.09$ | — | $1.36 \pm 0.22$ | — |
| 95% CI | — | 0.42–0.57 | | 1.18–1.55 | |
| BIS | $97 \pm 2$ | $84 \pm 8$ | < 0.001 | $67 \pm 14$ | < 0.001 |

Values are mean $\pm$ SD. There were no time effects on the propofol concentrations (analysis of variance [ANOVA]).

* Post hoc least significance test versus control.

$G_C$ = central carbon dioxide sensitivity; $G_P$ = peripheral carbon dioxide sensitivity; $G_{TOT}$ = total carbon dioxide sensitivity; NS = nonsignificant; CI = confidence interval; A, B, and C = samples before the first multifrequency binary sequence, between multifrequency binary sequences, and after the second multifrequency binary sequence.

loop, *i.e.*, at low $PET_{CO_2}$ ($\tau_{OFF}$); time delays of the central and peripheral chemoreflex loops ($T_C$ and $T_P$); and a linear trend term.[10] The noise corrupting the data was modeled through an external pathway with first-order dynamics.[10] Estimation of the parameters was performed with a one-step prediction error method.[15]

### Sensitivity Analysis

We performed an *a posteriori* sensitivity analysis. Sensitivity analysis enabled us to determine whether the parameter values could be estimated with finite precision from the actual data.[16–18] The analysis was performed by fixing one parameter (*i.e.*, by not allowing it to be estimated) at a time to a series of values (−100% to +100%) around the "optimum" value (in terms of the "cost" function or residual sum of squares of the difference between measured and estimated ventilation). The other parameters were estimated by minimizing the residual sum of squares. The shape of the relation between parameter and residual sum of squares informed us of whether parameters were estimable using the specific $PET_{CO_2}$ and $PET_{O_2}$ inputs.[16–18] Furthermore, because we performed the sensitivity analysis on actual data (and not on simulated data), we were informed of whether local minima existed.

### Statistical Analysis

The estimated parameters of control and propofol experiments were subjected to a one-way analysis of variance and *post hoc* least significant differences tests. *P* values less than 0.05 were considered to be significant. All values reported are mean $\pm$ SD.

## Results

All subjects terminated the protocol without side effects. Because of propofol, the arousal state of the subjects decreased with Bispectral Index values of $84 \pm 8$ at low-dose propofol infusion and $67 \pm 14$ at high-dose propofol infusion. The concentration of propofol remained constant over time during the two infusion schemes (table 1). Examples of a control and a propofol MFBS experiment (propofol target = 1.5 $\mu g/ml$) and model fits of one subject are given in figure 2. Only the deterministic part of the model is shown. It shows a large effect of propofol on the output of the central chemoreflex loop (a 55% reduction of $G_C$) with only a minor effect on the output of the peripheral chemoreflex loop (a 12% reduction of $G_P$).

The averaged model parameters are collected in table 1. At all three treatment levels, the estimated model parameters did not differ between the first and second $CO_2$ response. Propofol reduced the total $CO_2$ sensitivity ($G_{TOT}$) by approximately 20% at a propofol target of 0.75 $\mu g/ml$ and by approximately 34% at a target of 1.5 $\mu g/ml$. At both propofol concentrations, the reduction of $G_{TOT}$ was caused by a reduction of the output of the central chemoreflex loop by 20% and 40% at low- and high-dose propofol, respectively, without affecting the output of the peripheral chemoreflex loop. As a consequence, the ratio $G_P$ to $G_C$ is increased relative to the control state (fig. 3). The apneic threshold (B) showed a small but significant reduction during propofol infusion (table 1). The time constants and time delays of both chemoreflex loops remained unaffected by propofol (data not shown).

Figure 4 shows the results of the sensitivity analysis of the model parameters in one subject. A well-defined minimum of the residual sum of squares was observed for all parameters, indicating that they could be identified with acceptable accuracy (including parameters $T_P$ and $T_P$, not shown). The most accurately estimated parameters were B and $G_P$, as shown by the steepness of
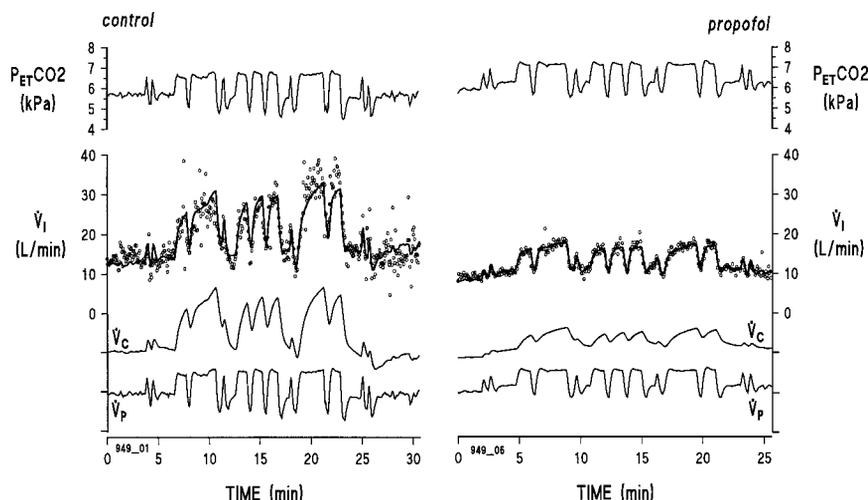
**Fig. 2. Control (*left*) and propofol (*right*) ventilatory responses to carbon dioxide of one subject. (*Top*) End-tidal partial pressure of carbon dioxide (PETco$_2$) input function is shown and is varied according to a multifrequency binary sequence that involved 13 steps into and 13 steps out of hypercapnia. (*Bottom*) Each circle represents one breath. The thick line through the breaths is the deterministic part of the model, which is the sum of the outputs of the peripheral ($\dot{V}_P$) and central ($\dot{V}_C$) chemoreflex loops and a trend term. Estimated control parameter values are as follows: B, 36.8 mmHg; G$_P$, 0.40 l · min$^{-1}$ · mmHg$^{-1}$; and G$_C$, 1.61 l · min$^{-1}$ mmHg$^{-1}$. Estimated propofol parameter values are as follows: B, 36.5 mmHg; G$_P$, 0.35 l · min$^{-1}$ · mmHg$^{-1}$; and G$_C$, 0.75 l · min$^{-1}$ · mmHg$^{-1}$. $\dot{V}_i$ = inspired minute ventilation.**

the increase in residual sum of squares at parameter values above and below the optimum. The shape of the curves for G$_C$, $\tau_P$, $\tau_{ON}$, and $\tau_{OFF}$ are markedly asymmetric, indicating that the estimation may be less accurate at values higher than the optimum. As expected, the steepness of the increase in the residual sum of squares of G$_P$ is less when this parameter is estimated from the single-step CO$_2$ input function (broken line in fig. 4). This indicates that G$_P$ is estimated with greater accuracy from an MFBS input function relative to a single-step input. G$_C$ is well-estimated from an MFBS and step input. However, the analysis indicates somewhat greater accuracy using a single CO$_2$ step for values above its optimum and an MFBS input for values below its optimum.
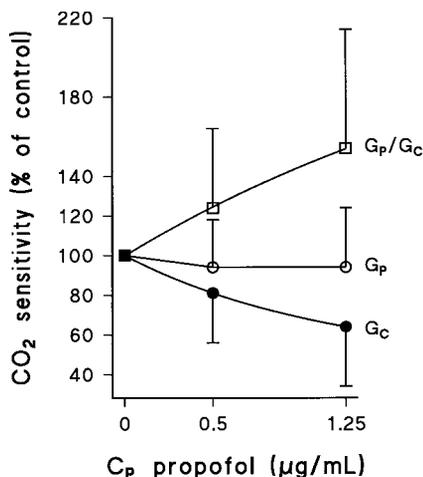


**Fig. 3. Influence of propofol on the ventilatory carbon dioxide (CO$_2$) sensitivities relative to control values for peripheral CO$_2$ sensitivity (G$_P$), central CO$_2$ sensitivity (G$_C$), and total CO$_2$ sensitivity (G$_{TOT}$). Values are mean ± SD.**

## Discussion

We used a multifrequency binary sequence in PETco$_2$ to quantify the effect of propofol on ventilatory control. The MFBS was designed by Pedersen *et al.*[12] to spread its power over the frequency range of interest for identification of both peripheral and central chemoreflex responses and to optimize identification of the peripheral chemoreflex response. Using a single step, the peripheral response is determined from only a limited portion of the data (2 min of the 15–20 min of a CO$_2$ study). Using an MFBS, this increases significantly (19.5 min of a 24-min experiment). Consequently, the precision of estimation parameters related to the peripheral chemoreflex loop is greater when derived from MFBS compared with single steps. Indeed, our sensitivity analysis indicates the improvement of the estimation of the peripheral CO$_2$ sensitivity compared with a step PETco$_2$ function, without compromising the accuracy of estimation of central CO$_2$ sensitivity (fig. 4).

We used a target-controlled infusion system to administer propofol. Fifteen minutes after target plasma concentrations of propofol were attained, the respiratory studies started. Estimation of the effect-site propofol concentration indicated that this time was ample for equilibrium between blood and effect site. We measured venous propofol concentrations, which may not reflect arterial or effect-site concentrations. However, we observed no time effect on venous propofol concentrations or on parameter estimates at P$_{low}$ or P$_{high}$. This indicates stable arterial and effect-site propofol concentrations and suggests a small gradient between venous and arterial propofol concentrations.
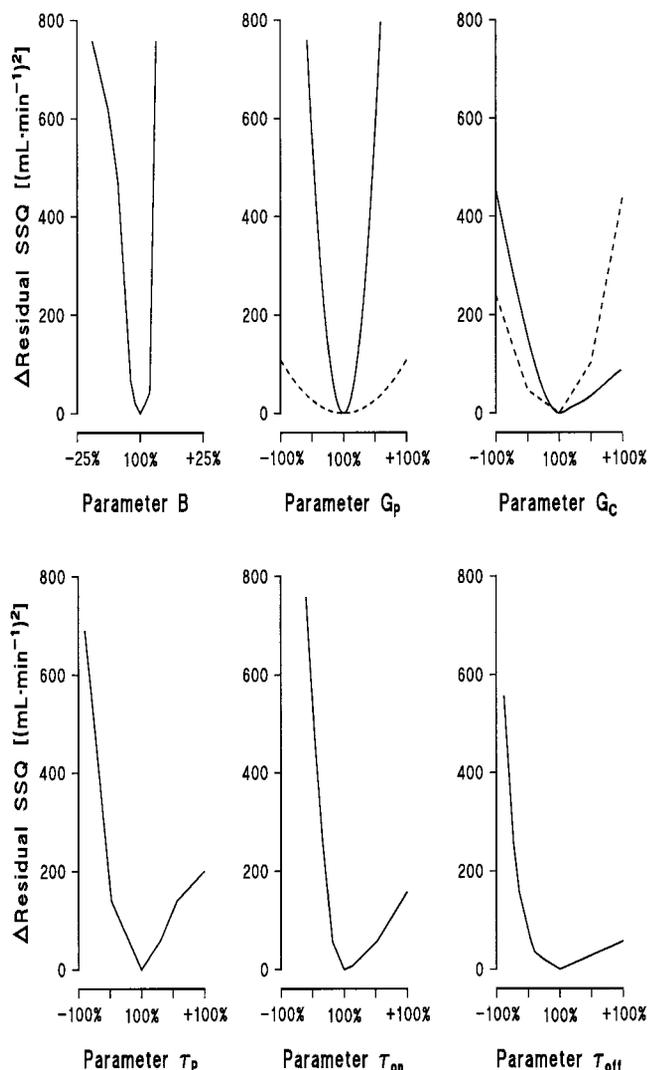
**Fig. 4. Results of the sensitivity analysis for the model parameters of the empirical carbon dioxide model of the ventilatory controller in one subject. The data are control data obtained using a multifrequency binary sequence input function (continuous lines). For comparative reasons, we added the sensitivity analysis on $G_P$ and $G_C$ obtained from a single step input function of the same subject (subject 936; broken lines). The x-axis gives the optimal parameter value (100%) ± 100%; the y-axis gives the increase in residual sum of squares ($\Delta$residual SSQ) from the optimal value (residual SSQ set at 0).**

With respect to the control of breathing, propofol may have an effect at the central or peripheral chemoreceptors, at the respiratory centers in the brainstem, at the neuromechanical link between brainstem and ventilation ($\dot{V}_i$), or at sites in the central nervous system involved in behavioral state control. The exact location of the central chemoreceptors is unknown, but they are probably located in the dorsomedial medulla, the rostroventrolateral medulla, or both.[19] The peripheral chemoreceptors are located in the carotid bodies, which are strategically situated at the bifurcation of the common carotid arteries and have an important role in oxygen delivery to the brain. The peripheral chemoreceptors

respond to changes in arterial oxygen tension ($Pa_{O_2}$) and arterial carbon dioxide tension ($Pa_{CO_2}$).[20,21]

We observed that propofol, at doses causing a decrease in Bispectral Index to approximately 70, has an important effect on the control of breathing. Specifically, propofol reduced $G_C$ but had little influence on $G_P$. This indicates the absence of a (selective) effect of low-dose propofol on the peripheral chemoreflex loop. In this respect, propofol stands in sharp contrast to the modern volatile halogenated anesthetics.[5-8] Our findings are in agreement with studies from the literature. Dow and Goodman[22] showed in humans that during propofol anesthesia, the carotid bodies retain their ability to respond to hyperoxia. In anesthetized cats, propofol displayed an inhibitory effect on areas of the dorsomedial and ventrolateral medulla, which possibly contain the central chemoreceptors.[19,23] Evidently, our data do not preclude some depressant effect of higher doses of propofol than used by us on the carotid bodies or its afferent pathways. For example, animal data show that high-dose propofol infusion, $18-35 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, causes the cessation of carotid body chemoreceptor activity.[24]

### Effect of Propofol on Peripheral $CO_2$ versus $O_2$ Responses

Our finding of the absence of an effect of propofol up to plasma concentrations of 1.25 $\mu$g/ml on the peripheral $CO_2$ response seems in disagreement with our previous observation of a 50% depression of the acute hypoxic $\dot{V}_i$ response by 0.6 $\mu$g/ml propofol.[2] Because the acute hypoxic ventilatory response originates at the peripheral chemoreceptors of the carotid bodies,[25] some depression of the peripheral $CO_2$ response was anticipated from our earlier results. Apart from the possibility that $O_2$ and $CO_2$ sensing at the carotid bodies are differentially affected by propofol, there are three conceivable explanations for this discrepancy.

First, carotid body depression by anesthetics is dependent on stimulus intensity. For example, Ponte and Sadler[26] showed that relative to a mild hypoxic stimulus, a more intense stimulus (partial pressure of oxygen [$P_{O_2}$] < 40 mmHg) is able to overcome volatile anesthetic-induced depression of the carotid bodies. In analogy, the stimulus in this study (a hypercapnic–hypoxic stimulus of a $PET_{CO_2}$ of 13 mmHg above resting and an $Sp_{O_2}$ of 88–90%) may offset depression of the carotid bodies by propofol as observed previously using a less-intense hypoxic stimulus (a hypercapnic–hypoxic stimulus of a $PET_{CO_2}$ of 5 mmHg above resting and an $Sp_{O_2}$ of ∼87%). Interestingly, when assessing the effect of low-dose volatile anesthetics on ventilatory control, we observed depression of carotid body–mediated responses even when intense stimuli, such as used in this study, were applied.[6,8] This suggests a difference in stimulus inten-

sity needed to overcome carotid body depression caused by propofol and volatile anesthetics.

Second, in cats, Berkenbosch *et al.*[21] studied the peripheral $\dot{V}_i$ response dynamics to hypoxic stimulation while the Pao$_2$ of the medulla oblongata was kept constant using the technique of artificial brainstem perfusion. Mathematically, the responses were best described by two components: a fast component with a time constant of approximately 2 s and a slow component with a time constant of approximately 73 s. The fast component was considered to originate at the carotid bodies, whereas it was argued that the slow component was due to central modulation of the carotid body response (*i.e.*, neuronal dynamics).[21] Interestingly, in the same animal preparation, the response of the peripheral chemoreflex pathway to changes in PET$_{CO_2}$ does not show a slow component.[21] This indicates that although peripheral hypoxic stimulation activates central neuronal dynamics, peripheral hypercapnic stimulation does not. Also, in humans, the hyperventilatory response to hypoxia is well-described by a fast and a slow component.[27] We previously studied the effect of 0.6 $\mu$g/ml propofol on the ventilatory responses to 3 min hypoxic pulses[2] and reanalyzed the data using the two-component model as described by Berkenbosch *et al.*[21] All control curves were best described by two components as judged by the Akaike criterion,[28] with time constants of 3 and 100 s for the fast and slow components, respectively. Propofol did not affect the gain (*i.e.*, hypoxic sensitivity) of the fast component (G$_{propofol}$/G$_{control}$ = 0.95), but caused a significant reduction of the gain of the slow component (G$_{propofol}$/G$_{control}$ = 0.45; $P < 0.05$). If we assume that the fast response reflects the carotid body response to hypoxia and the slow component central neuronal dynamics,[21,29] these results suggest that propofol affects central neuronal dynamics but has little effect on the carotid bodies or their output, and thus does not reduce G$_p$. This is in contrast to the effect of inhalational anesthetics. We previously studied the effect of sevoflurane, 0.25% end-tidal (~0.15 MAC), on the ventilatory responses to 3-min hypoxic pulses[8] and reanalyzed the data using the two-component model as described above. Sevoflurane reduced the fast and slow component by 25 and 60%, respectively ($P < 0.05$), an indication for an effect of sevoflurane on the carotid bodies and on central neuronal dynamics.

Third, apart from a stimulatory effect at the carotid bodies, hypoxia causes depression of ventilation *via* central mechanisms, *i.e.*, within the central nervous system.[30] The central effect of hypoxia on $\dot{V}_i$ is already apparent after 1 min of hypoxic exposure[29]; therefore, any measured hypoxic $\dot{V}_i$ response is the mixture of carotid body and central effects on $\dot{V}_i$. Because propofol enhances the magnitude of the central depressant effects of hypoxia in humans,[2] greater depression by propofol

of the measured ventilatory response to hypoxia relative to the measured peripheral CO$_2$ response is expected.

These three mechanisms should be taken into account when comparing our current results on the effect of propofol on the peripheral and central chemoreflex loops with studies from the literature on the effect of propofol on the ventilatory response to acute [2,31] and subacute hypoxia.[32]

### *Influence of Propofol* versus *Inhalational Anesthetics on Peripheral CO$_2$ Response*

The discrepant effects of propofol and sevoflurane on the carotid body response to CO$_2$ is striking and may be explained by differences in molecular sites of action of intravenous and halogenated inhalational anesthetics. We believe that propofol, like inhalational anesthetics, affects breathing through enhancement of $\gamma$-aminobutyric acid–mediated transmission and reduction of glutamatergic activity in the brainstem.[2,33] This may have induced the depression of G$_C$ in our study. Furthermore, inhalational anesthetics activate background K$^+$ channels in the peripheral and central nervous system.[34–36] These channels are involved in tonic inhibition of cellular excitability, and activation by volatile anesthetics may be the cause of some major side effects, such as depression of cardiac function and respiratory depression. Buckler *et al.*[36] recently showed the existence of an oxygen-, acid-, and inhalational anesthetic (halothane)–sensitive background K$^+$ channel in the carotid body chemoreceptor cells, which possibly is an important link in the cascade leading to CO$_2$ and O$_2$ sensing in the carotid bodies and the selective site of inhalational anesthetic depression of carotid body function. Further studies are needed to show how anesthetics (including propofol) modulate the pH–Po$_2$ sensitivity of these background channels.

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