

Propofol for Monitored Anesthesia Care

Implications on Hypoxic Control of Cardiorespiratory Responses

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Background: Hypoxia has a dual effect on ventilation: an initial period of hyperventilation, the acute hypoxic response, is followed after 3–5 min by a slow decline, the hypoxic ventilatory decline. Because of hypoxic ventilatory decline, subsequent acute hypoxic responses are depressed. In this study, the influence of a sedative concentration of propofol on ventilation was studied if hypoxia was sustained and intermittent.

Methods: Ten healthy young male volunteers performed two hypoxic tests without and with a target controlled infusion of propofol. The sustained hypoxic test consisted of 15 min of isocapnic hypoxia followed by 2 min of normoxia and 3 min of hypoxia. The test of hypoxic pulses involved six subsequent exposures to 3 min hypoxia followed by 2 min of normoxia. The bispectral index of the electroencephalogram was measured to obtain an objective measure of sedation.

Results: Blood propofol concentrations varied among subjects but were stable over time (mean blood concentration 0.6 $\mu\text{g}/\text{ml}$). The sustained hypoxic test showed that propofol decreased acute hypoxic response by ~50% and that the magnitude of hypoxic ventilatory decline relative to acute hypoxic response was increased by > 50%. Propofol increased the depression of the acute hypoxic response after 15 min of hypoxia by ~25%. In control and propofol studies, no hypoxic ventilatory decline was generated during exposure to hypoxic pulses. The bispectral index–acute hypoxic response data suggest that subjects were either awake (with minimal effect on acute hypoxic response) or sedated (with 50–60% reduction of acute hypoxic response).

Conclusions: The depression of acute hypoxic response results from an effect of propofol at peripheral or central sites involved in respiratory control or secondary to the induction of

sedation or hypnosis by propofol. The relative increase in hypoxic ventilatory decline is possibly related to propofol's action at the γ -aminobutyric acid A (GABA_A) receptor complex, causing increased GABAergic inhibition of ventilation during sustained (but not intermittent) hypoxia. (Key words: Bispectral index; carotid bodies; control of breathing; respiration.)

DURING monitored anesthesia care, in which anesthetics or analgesics are used as adjuvant to regional anesthesia, ventilatory control is predominantly metabolic or chemical in nature. Because hypoxia (especially episodic or intermittent hypoxia) is frequently associated with monitored anesthesia care,^{1,2} we investigated the influence of propofol, a popular hypnotic for sedation during such care, on the ventilatory responses to acute, sustained, and episodic isocapnic hypoxia.

Hypoxia has a dual effect on the ventilatory control system. A short episode of hypoxia (duration < 5 min) causes an increase in the hypoxic drive from the peripheral chemoreceptors of the carotid bodies.³ Hypoxia of longer duration causes depression of the respiratory centers in the brain stem.^{3,4} The net effect of these opposing phenomena is that the ventilatory response to sustained hypoxia is biphasic: An initial period of hyperventilation, the acute hypoxic response (AHR), is followed within 3 to 5 min by a slow hypoxic ventilatory decline (HVD). A steady state in ventilation (\dot{V}_i) is obtained after 15 to 20 min.^{5,6} The mechanism of the hypoxic depression of \dot{V}_i (HVD) is unknown. During moderate hypoxia (oxygen saturation 80–90%) the accumulation and release of inhibitory neurotransmitters or modulators, such as γ -aminobutyric acid (GABA) or adenosine, is thought to play a major role in the development of HVD.^{5–9} A consequence of the hypoxia-related central depression is that the recovery of the hypoxic response is not immediate (*i.e.*, after prolonged hypoxia subsequent hypoxic responses remain depressed).^{5,6}

Recent studies indicate that several general anesthetics, including propofol, interact with or modulate the GABA_A receptor complex.^{10–12} At clinical concentrations, propofol enhances GABA-evoked chloride cur-

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rents and causes direct activation of the receptor in the absence of GABA.^{11,12} GABA_A receptors are thought to be involved in the generation of HVD,^{3-6,8} and hence there may be an important role for propofol in modulating or enhancing HVD.

Clinically, hypoxia is often episodic or periodic, especially during sleep or sedation.^{2,13} We therefore further examined the interaction of propofol and periodic hypoxia on \dot{V}_i and the development of HVD. Apart from assessing ventilatory responses, we measured heart rate responses and the bispectral index (BIS) of the electroencephalogram (EEG). The BIS informs us on the central nervous system arousal state of the participants, which is relevant because it may be an important factor in the study outcome.

Subjects and Methods

Ten healthy male volunteers (aged 18–25 yr) participated in the protocol after approval was obtained from the Leiden University Medical Center Human Ethics Committee. The subjects were healthy and did not have histories of tobacco or illicit drug use. They were instructed not to eat or drink for at least 8 h before the study.

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 standard electrodes for EEG measurement (BisSensor, Aspect Medical Systems, Natick, MA) were placed and the subjects rested for 20 to 30 min. Next a face mask was applied over the mouth and nose. Subjects were in a comfortable semirecumbent position. The inspired and expired gas flows were measured with a pneumotachograph connected to a pressure transducer and electronically integrated to yield a volume signal. Corrections were made for the changes in gas viscosity resulting from changes in oxygen concentration of the inhaled gas mixtures. The pneumotachograph was connected to a T piece. One arm of the T piece received a gas mixture from a gas mixing system consisting of three mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands). A personal computer provided control signals to the mass-flow controllers so that the composition of the inspired gas mixtures could be adjusted to force end-tidal pressures of oxygen (P_{ET,O_2}) and carbon dioxide (P_{ET,CO_2}) to follow a specified pattern in time.¹⁴ The inspired and expired gas concentrations and the arterial hemoglobin-oxygen

saturation (Sp_{O_2}) were measured with a Datex Multicap gas monitor and Datex Satellite Plus pulse oximeter, respectively (Datex-Engstrom, Helsinki, Finland). The EEG and electromyogram were recorded using an Aspect (Natick, MA) A-2000 EEG monitor. The monitor computed the BIS over 4-s epochs. We averaged the BIS values over 1-min intervals.

Study Design

Two different hypoxic tests (sustained hypoxia and hypoxic pulses) were performed without and with propofol. Control studies preceded propofol studies. The order of hypoxic tests was randomized. Between tests there was ample time for resting. Control and drug hypoxic studies were performed at identical P_{ET,CO_2} s, 5–7 mmHg above awake resting values. This was done to balance an effect of the increase in P_{ET,CO_2} resulting from depression of \dot{V}_i by propofol.

Sustained Hypoxic Test. The P_{ET,O_2} was forced as follows: (1) 10 min at 110 mmHg, (2) a rapid decrease to 50 mmHg, (3) 15 min at 50 mmHg, (4) a rapid increase to 110 mmHg, (5) 2 min at 110 mmHg, (6) a rapid decrease to 50 mmHg, (7) 3 min at 50 mmHg, and (8) at least 5 min at more than 300 mmHg.

Hypoxic Pulses. The P_{ET,O_2} waveform was as follows: (1) 10 min at 110 mmHg, (2) a rapid decrease to 50 mmHg, (3) 3 min at 50 mmHg, (4) a rapid increase to 110 mmHg, and (5) 2 min at 110 mmHg. The hypoxic-normoxic sequence (steps 2–5) was repeated five times. This procedure yields six 3-min hypoxic pulses separated by 2 min of normoxia.

Propofol Administration, Sampling, and Assay. A Psion (London, United Kingdom) palm-top computer programmed with a three-compartment propofol pharmacokinetic data set¹⁵ was used to control a Becton Dickinson infusion pump (St. Etienne, France) for the intravenous administration of propofol. The propofol target concentration was set at 1 $\mu\text{g}/\text{ml}$ and was kept constant during both propofol hypoxic studies. After BIS values had reached a steady level, but at least 20 min after the target had been reached, the hypoxic studies started. Propofol blood samples (5 ml) were obtained 5 min before the first hypoxic study (T_1), at the end of the first hypoxic study (T_2) and at the end of the second hypoxic study (T_3). The samples were collected in syringes containing potassium oxalate. The propofol concentrations were determined by reverse-phase high-performance liquid chromatography.¹⁶

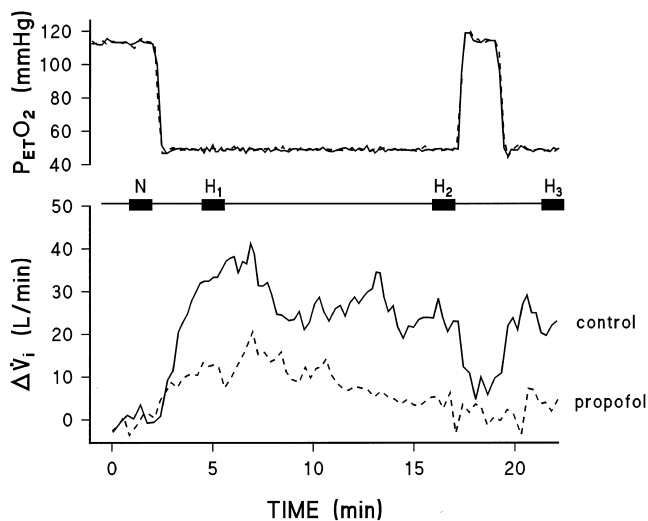


Fig. 1. Control and propofol ventilatory responses to the sustained hypoxic test of one subject. (*Top*) The end-tidal pressure of oxygen input to the subject. (*Bottom*) The ventilatory responses above normoxic baseline (\dot{V}_i data are averaged over six breaths). Period N is the 1-min period before the 15 min of hypoxia, period H₁ the third minute of hypoxia, period H₂ the 15th minute of hypoxia, and period H₃ the third minute of the second hypoxic bout. Continuous line = control; dashed line = propofol.

Data Analysis

Sustained Hypoxic Test. Mean values of the breath-to-breath data were chosen over identical time segments (see fig. 1). Period N is the 1-min period before the 15-min of hypoxia, period H₁ the third minute of hypoxia, period H₂ the 15th minute of hypoxia, and period H₃ the third minute of the second hypoxic bout. Differences in \dot{V}_i between periods N and H₁ were defined as the first AHR (AHR₁), between periods N and H₂ as the sustained hypoxic response, and between periods N and H₃ as the second AHR (AHR₂). The difference between AHR₁ and sustained hypoxic response was used as measure of the HVD. The \dot{V}_i responses are expressed as the change in \dot{V}_i per percentage change in SpO₂ (unit: $l \cdot \text{min}^{-1} \cdot \%^{-1}$).

Hypoxic Pulses. We tested the occurrence of HVD by comparing the hypoxic response to the first hypoxic pulse with the response to the last hypoxic pulse. In order to do so, mean values of the breath-to-breath data of the last minute of normoxia before the first hypoxic pulse (period A) and the third minute of the first (period B) and last hypoxic pulse (period C) were calculated. Differences in \dot{V}_i between periods A and B were defined as the first AHR (AHR_{first}), and between periods A and C as the last AHR (AHR_{last}).

Statistical Analysis

A two-way analysis of variance was performed on the different periods (N, H₁, H₂, and H₃) of the sustained hypoxic test. Because peak heart rate responses occurred at period H₁ + 3 min (see Results), for hypoxic heart rate sensitivities a comparison was made among periods H₁ + 3 min, H₂, and H₃. Differences between periods were tested with the Student-Newman-Keuls test. A paired *t* test was performed to compare ventilatory and heart rate responses to the first and sixth hypoxic pulses. To detect the significance of difference between the control and propofol studies, a paired *t* test was performed on individual parameters of the hypoxic studies. *P* values < 0.05 were considered significant. All values are mean ± SD.

Results

Propofol Concentrations and Bispectral Index Values

Blood propofol concentrations and BIS values varied considerably among subjects but were constant over time within subjects. Over time, blood propofol concentrations were $0.61 \pm 0.30 \mu\text{g/ml}$ at T₁, $0.56 \pm 0.23 \mu\text{g/ml}$ at T₂, and $0.58 \pm 0.23 \mu\text{g/ml}$ at T₃ (not significant). Mean coefficient of variation over time was 14.6% (range, 7–34%). Because of technical problems, the collection of BIS data was not achieved in one subject. Averaged control BIS values were 97 ± 2 and 96 ± 2 for the sustained hypoxic and hypoxic pulses studies, respectively. During propofol, the mean BIS values were 76 ± 14 for the sustained hypoxic study (range among subjects, 53–91; mean coefficient of variation over time, 7%), and 76 ± 10 for the hypoxic pulses study (range among subjects, 66–91; mean coefficient of variation over time, 8%).

Ventilatory Responses

Sustained Hypoxic Test. Propofol reduced normoxic baseline \dot{V}_i by approximately 15% (*P* < 0.001; table 1). In figure 1, examples of a control and propofol hypoxic study of one subject are shown. In all subjects, in both control and propofol studies, the hypoxic ventilatory responses were biphasic and the recovery of the hypoxic response was not immediate (figs. 1 and 2, table 1). Propofol decreased AHR₁ by 50% from 1.74 ± 1.22 to $0.89 \pm 0.70 l \cdot \text{min}^{-1} \cdot \%^{-1}$ (*P* < 0.001), the sustained hypoxic response by 60% from 1.11 ± 0.80 to $0.33 \pm 0.30 l \cdot \text{min}^{-1} \cdot \%^{-1}$ (*P* = 0.002), and AHR₂ by 60% from

PROPOFOL, HYPOXIA, AND \dot{V}_i **Table 1. Ventilatory, Heart Rate, and Bispectral Index Responses to Sustained Hypoxia before and during Propofol Administration**

	Period			
	N	H ₁	H ₂	H ₃
\dot{V}_i (l/min)				
Control	19.2 ± 5.2	37.6 ± 14.4*	31.0 ± 11.3†	30.8 ± 11.1†
Propofol	16.0 ± 8.4	25.4 ± 13.3*	19.8 ± 10.0†	20.4 ± 10.9†
\dot{V}_i (% of baseline \dot{V}_i)				
Control	100	195 ± 54*	162 ± 28†	158 ± 21†
Propofol	100	160 ± 29*	127 ± 16†	127 ± 10†
V_T (ml/breath)				
Control	1145 ± 201	1755 ± 296*	1578 ± 305†	1559 ± 324†
Propofol	913 ± 368	1287 ± 426*	1104 ± 373†	1097 ± 371†
f (breaths/min)				
Control	17 ± 4	22 ± 10*	20 ± 6	20 ± 6
Propofol	16 ± 3	19 ± 5*	17 ± 3‡	18 ± 4‡
Heart rate (beats/min)				
Control	69 ± 10	83 ± 16*	83 ± 14*	81 ± 12*
Propofol	58 ± 11	68 ± 16*	68 ± 15*	66 ± 14*
BIS				
Control	96 ± 2	97 ± 1	97 ± 2	97 ± 2
Propofol	78 ± 11	79 ± 9	74 ± 19	74 ± 17
PET _{CO₂} (mmHg)				
Control	46.8 ± 2.9	46.6 ± 3.0	46.9 ± 3.0	46.7 ± 2.9
Propofol	46.6 ± 2.7	46.5 ± 3.1	46.8 ± 2.9	46.7 ± 2.9
PET _{O₂} (mmHg)				
Control	112.0 ± 0.8	49.1 ± 0.8*	49.1 ± 0.4*	49.0 ± 0.8*
Propofol	112.8 ± 1.1	49.1 ± 0.5*	48.4 ± 0.4*	49.0 ± 0.7*
Sp _{O₂} (%)				
Control	98 ± 1	87 ± 4*	87 ± 4*	87 ± 4*
Propofol	98 ± 1	86 ± 4*	85 ± 3*	86 ± 3*

Values are mean ± SD.

N = the last normoxic minute before the 15-min hypoxic period; H₁ = the third minute of initial hypoxia; H₂ = the 15th minute of initial hypoxia; H₃ = the third minute of the second hypoxic episode; \dot{V}_i = minute ventilation; V_T = tidal volume; f = respiratory frequency; BIS = bispectral index; PET_{CO₂} = end-tidal carbon dioxide partial pressure; PET_{O₂} = end-tidal oxygen partial pressure; Sp_{O₂} = oxygen saturation as measured by pulse oximetry.

* $P < 0.05$ vs. period N.

† $P < 0.05$ vs. periods N and H₁.

‡ $P < 0.05$ vs. period H₁.

1.04 ± 0.48 to 0.39 ± 0.33 l · min⁻¹ · %⁻¹ ($P < 0.001$). The absolute magnitude of HVD did not differ between control and propofol (0.63 ± 0.51 vs. 0.56 ± 0.52 l · min⁻¹ · %⁻¹, not significant). Propofol increased the ratio HVD/AHR₁ by > 50%, from 0.35 ± 0.16 to 0.54 ± 0.16 ($P = 0.02$) and caused more depression of the second hypoxic response: The ratio AHR₂/AHR₁ was 0.67 ± 0.16 for control and 0.51 ± 0.22 for propofol ($P < 0.05$).

Hypoxic Pulses. BIS values and control of end-tidal gas concentrations are listed in table 2. In figure 3, examples of a control and propofol study of one subject are shown. In the control study, \dot{V}_i in periods B and C increased to 197 ± 78% and 200 ± 63% of baseline,

respectively. Corresponding values in the propofol study were 154 ± 27% (period B) and 144 ± 37% (period C). In control and propofol studies AHR_{first} did not differ from AHR_{last}: control, 1.35 ± 0.84 versus 1.35 ± 0.67 l · min⁻¹ · %⁻¹ (not significant; fig. 4); propofol, 0.64 ± 0.39 versus 0.58 ± 0.25 l · min⁻¹ · %⁻¹ (not significant).

Heart Rate Responses

Because of technical problems, the collection of heart rate data failed in one subject. Propofol decreased normoxic heart rate by 8–10 beats/min (table 1). In control and propofol sustained hypoxic studies, peak heart rate responses occurred at period H₁ + 3 min (fig. 2). Control heart rate sensitivity decreased from its peak by 20%

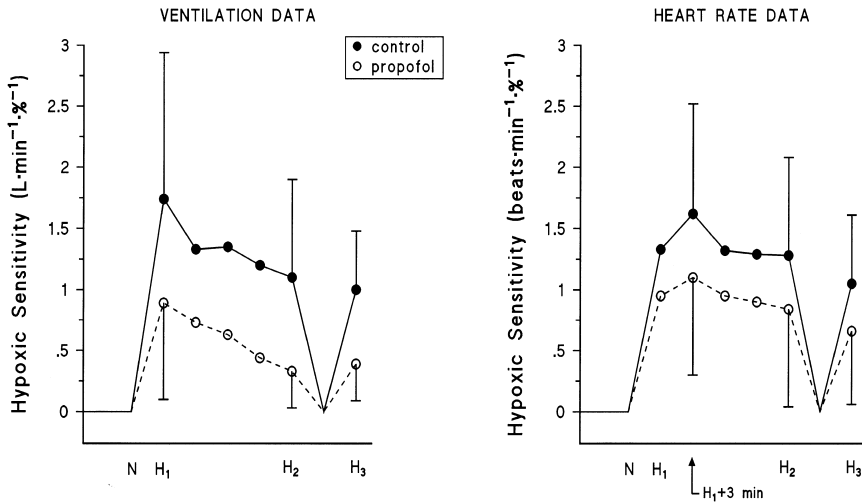


Fig. 2. The mean ventilatory (left) and heart rate (right) responses to the sustained hypoxic test expressed as change in \dot{V}_i or heart rate per percent in arterial hemoglobin-oxygen saturation (Sp_{O_2}). For periods N, H₁, H₂, and H₃ see legend of figure 1. The data points between periods H₁ and H₂ are 1-min averages of minutes 6 (i.e., H₁ + 3 min), 9, and 12 of hypoxia. Values are mean \pm SD.

in period H₂ (not significant) and by 35% in period H₃ ($P < 0.05$). Propofol heart rate sensitivity decreased from its peak by 21% in period H₂ ($P < 0.05$) and by 38% in period H₃ ($P < 0.05$). Compared with control, propofol decreased hypoxic heart rate sensitivities in periods H₁ + 3 min, H₂, and H₃ by $27 \pm 36\%$, $36 \pm 22\%$, and $38 \pm 34\%$, respectively (not significant). Heart rate responses during the hypoxic pulses test did not differ between the first and sixth hypoxic pulse and between control and propofol studies.

Table 2. Control of End-tidal Oxygen and Carbon Dioxide Partial Pressures, Oxygen Saturation, and Bispectral Index Values during the Hypoxic Pulses Test

	Period		
	A	B	C
PET _{CO₂} (mmHg)			
Control	46.5 \pm 3.0	46.5 \pm 3.1	46.5 \pm 3.1
Propofol	46.7 \pm 3.0	46.6 \pm 3.2	46.5 \pm 3.0
PET _{O₂} (mmHg)			
Control	113.3 \pm 1.4	49.5 \pm 0.6*	49.1 \pm 0.6*
Propofol	112.5 \pm 0.6	48.8 \pm 0.3*	48.7 \pm 0.7*
Sp _{O₂} (%)			
Control	98 \pm 1	86 \pm 3*	86 \pm 3*
Propofol	98 \pm 1	86 \pm 2*	86 \pm 3*
BIS			
Control	96 \pm 1	96 \pm 1	96 \pm 2
Propofol	76 \pm 10	76 \pm 10	77 \pm 14

Values are mean \pm SD.

A = the last minute of normoxia before the first hypoxic pulse; B = the third minute of the first hypoxic pulse; C = the third minute of the sixth hypoxic pulse; BIS = bispectral index; PET_{CO₂} = end-tidal carbon dioxide partial pressure; PET_{O₂} = end-tidal oxygen partial pressure; Sp_{O₂} = oxygen saturation as measured by pulse oximetry.

* $P < 0.05$ vs. period A.

Discussion

Influence of Propofol on the Ventilatory Response to Acute Hypoxia

In this study we observed that, in a healthy, young group of male volunteers, propofol, at a sedative con-

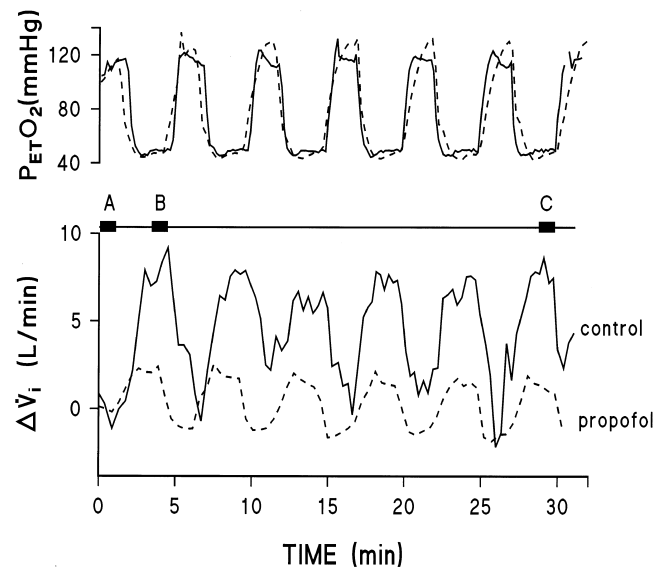


Fig. 3. Control and propofol ventilatory responses to intermittent 3-min hypoxic episodes (six hypoxic pulses) of one subject. In between hypoxia there are 2-min normoxic periods. (Top) The end-tidal pressure of oxygen input to the subject. (Bottom) The ventilatory responses above normoxic baseline (\dot{V}_i data are averaged over six breaths). Period A is the 1-min period before the first hypoxic episode; period B is the third minute of the first hypoxic episode; period C is the third minute of 6th hypoxic episode. Control = continuous line; propofol = dashed lines.

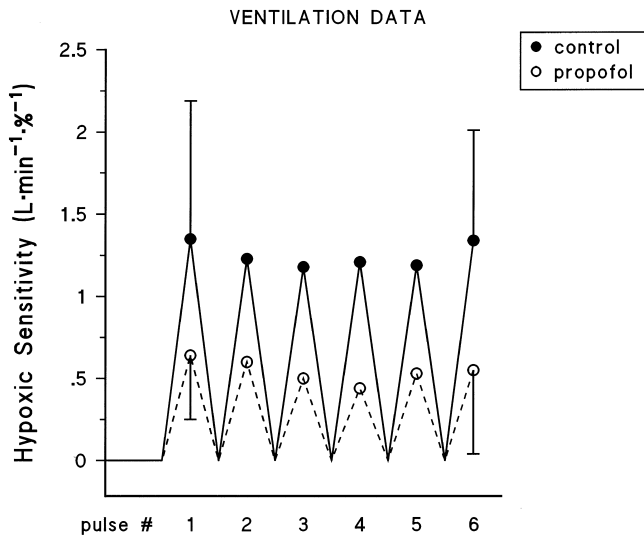


Fig. 4. The mean ventilatory responses to hypoxic pulses expressed as change in \dot{V}_i per percentage in arterial hemoglobin-oxygen saturation (Sp_{O_2}). Hypoxic duration of each pulse is 3 min. For both control and propofol, the response to the last hypoxic pulses (no. 6) is not different from the response to the first pulse. Values are mean \pm SD.

centration (mean BIS value 76), caused a \sim 50% reduction of the ventilatory response to acute hypoxia. Two previous studies examined the influence of propofol on the hypoxic ventilatory response. Blouin *et al.*¹⁷ tested the influence of propofol at a blood concentration of 2 μ g/ml on a ramp hypoxic test. They observed an 80% depression of the ventilatory response in eight male volunteers. However, because the ramp hypoxic test is a mixture of AHR and HVD,¹⁸ their finding is best compared with our observation of propofol-induced reduction of the sustained hypoxic response by about 60%. Nagyova *et al.*¹⁹ showed a reduction of the AHR by 21, 23, and 60% at respective propofol blood concentrations of 0.5, 1, and 2 μ g/ml. This is less than our finding of 50% depression at 0.6 μ g/ml. However, in the study by Nagyova *et al.*, differences between the level of consciousness in awake and drug studies were minimized by encouraging the subjects to watch television. There is now ample evidence that this induces behavioral control of breathing. As a consequence, additional (nonchemical) drives increase responses mediated *via* the carotid bodies.²⁰

Our study gives little information on the site of action of propofol with respect to its effects on normoxic resting ventilation and AHR. Propofol may affect ventilatory control at four possible sites: at the peripheral or central chemoreceptors; at the respiratory centers in the

brain stem; at the neuromechanical link between brain stem and ventilation (this includes spinal motoneurons, respiratory muscles, lungs, and airways); at sites in the central nervous system involved in behavioral-state control (for example the brain stem reticular system). In cats and rabbits, Ponte and Sadler²¹ showed that a high-dose propofol infusion (18–35 mg/kg \cdot h) into the carotid artery abolished chemoreceptor discharge in normoxia and prevented an increase during hypoxia. In humans, Dow and Goodman²² showed that during propofol anesthesia, sudden exposure to hyperoxia reduces \dot{V}_i . This suggests that the peripheral chemoreceptors remain active during propofol anesthesia but does not exclude some depression. In anesthetized cats, an inhibitory effect of propofol on cells in the dorsomedial and ventrolateral medulla mediating pressor effects has been observed.²³ Both sites are involved in respiratory control and may contain central chemoreceptors.²⁴ We suggest that, in our study, propofol decreased AHR by depression of the peripheral chemoreflex loop, either directly by enhancing GABAergic inhibition of respiratory centers within the brain stem or indirectly by changing the behavioral state of the subjects. At this time, we are unable to exclude an effect of propofol at the peripheral chemoreceptors.

The EEG data give some evidence for an effect of propofol on ventilatory control *via* sites involved in behavioral-state control. We used the BIS of the EEG as measure of the state of sedation or hypnosis. Among subjects we observed a large variability in blood propofol concentrations and BIS values. We relate this to the relatively large interindividual variability in pharmacokinetics and dynamics of intravenous anesthetics. For the BIS, we relate this further to the occurrence, at least in some subjects, of natural sleep on top of drug-induced sedation. Non-rapid eye movement and slow-wave sleep cause further decreases in BIS.²⁵ In figure 5, we plotted the BIS values of individual subjects (*x*-axis) *versus* the depression of the AHR (*y*-axis, AHR as percentage of control and obtained from both hypoxic studies). The data suggest the existence of two (behavioral and respiratory) states in our subjects. Subjects were either awake (control studies [open squares in the right part of fig. 5]) and propofol studies with little to no effect on AHR [open circles in the right part of fig. 5]) or sedated or asleep with 50–60% depression of AHR (closed circles in the right part of fig. 5). In the latter group, variations in the level of sedation or hypnosis (as measured by the BIS) had little further effect on AHR.

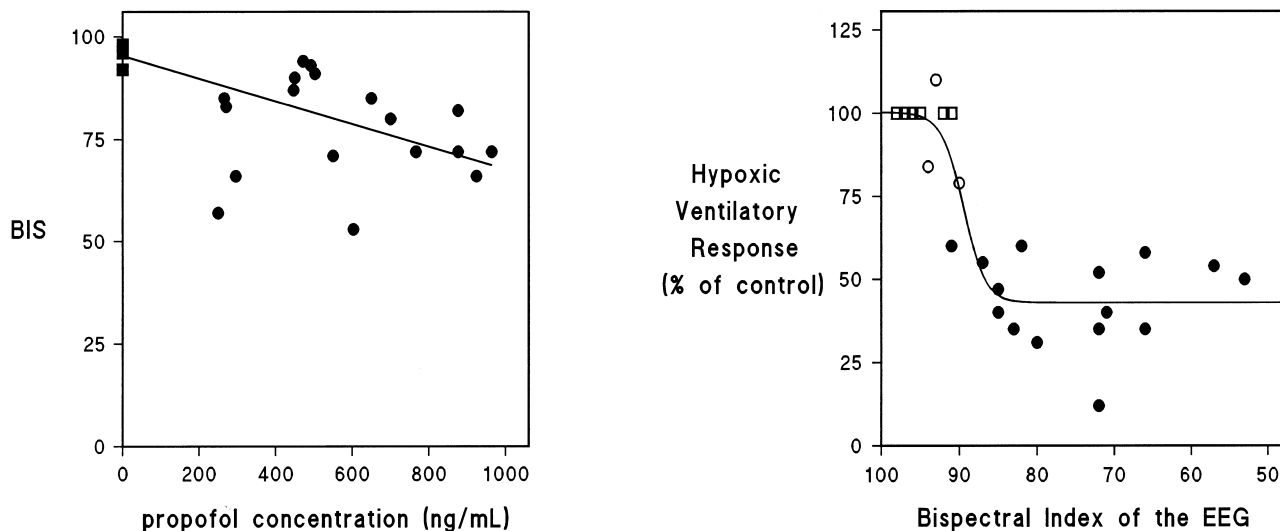


Fig. 5. (Left) The relationship between blood propofol concentration and bispectral index (BIS). Note the twofold larger range in propofol concentration data compared with BIS data. The squares are data points obtained before propofol administration, the circles during propofol infusion. The line through the data is linear regression. (Right) Influence of the sedative or hypnotic state as measured by the BIS of the electroencephalogram on the depression by propofol of the acute hypoxic ventilatory response (expressed as percentage of awake values). Squares = control data; open circles = propofol data in "awake" subjects as judged by their BIS values and acute hypoxic response. To guide the eye, a sigmoid function (the Hill equation) was fitted to the data. The BIS value at which 50% of the effect occurred is 89.

Influence of Propofol on HVD

In humans, the mechanism of the secondary decline in \dot{V}_i during hypoxia of longer duration (> 3 min) is still under debate. The following observations with respect to HVD are of importance to our study and may provide some insight into the mechanism of HVD:

1. Moderate hypoxia causes an increase in cerebral blood flow (CBF).²⁶ Because of the increase in CBF, the carbon dioxide tension within the central nervous system and hence the central ventilatory drive are decreased. As a consequence a significant part of HVD may be related to an increase in CBF.
2. When HVD develops, its influence on \dot{V}_i does not dissipate immediately upon the termination of hypoxia. Subsequent hypoxic responses remain depressed (ratio $AHR_2/AHR_1 < 1$), and 1 h of air breathing is necessary for a full recovery of AHR ($AHR_2/AHR_1 = 1$).^{5,6} These observations have led to the hypothesis that the accumulation or release of neurotransmitters or modulators with net inhibitory influences on \dot{V}_i is quantitatively the more important contributor to HVD. The most important neurotransmitter candidates are GABA and adenosine.^{3-6,8,9} On the termination of hypoxia, their turnover is not immediate, and therefore the depressant effects of hypoxia wane slowly. Animal studies give further proof

for a role of central inhibition from GABA. Bicuculline, a GABA_A receptor antagonist, reverses HVD in the anesthetized cat.⁹

3. Among and within subjects, the ratio HVD/AHR₁ is constant with changing values of AHR₁.^{5,6} This is explained by a modulatory effect of the hypoxic drive of the peripheral chemoreceptors on the central (*i.e.*, within the central nervous system) development of HVD.⁶

In our study, propofol did not affect the absolute magnitude of HVD. However, relative to AHR₁, HVD did increase, causing an increase in ratio HVD/AHR₁. Furthermore, the ratio AHR₂/AHR₁ decreased during propofol infusion. Because propofol concentrations and BIS values were constant over time, we argue that these observations indicate that propofol enhanced the development of HVD. Recent studies indicate that propofol acts at GABA_A receptors and enhances GABA-ergic transmission.^{11,12,27} We therefore suggest that the relative increase in HVD is related to propofol's action at the GABA_A receptor complex. Other GABA_A receptor agonists such as midazolam cause similar effects on the ratio HVD/AHR₁.⁸ Although these observations support a role for GABAergic neurons in the inhibition of brain stem respiratory centers during sustained hypoxia, they do not exclude the involvement of other receptor systems

such as adenosine and opioid receptors. For example, Cartwright *et al.*²⁸ showed an increase of the ratio HVD/AHR₁ by the μ receptor agonist alfentanil. Aminophylline, an adenosine-receptor blocker, reduces the ratio HVD/AHR₁.⁷ These findings illustrate that HVD development is modulated by various agents commonly used in anesthesia. Studies in humans on the influence of propofol on CBF indicate that propofol reduces CBF concomitant with a reduction in cerebral metabolic rate and maintains the cerebrovascular response to changes in arterial PCO₂.²⁹ Although no studies on the influence of propofol on changes in arterial oxygen partial pressure are available, it seems improbable that propofol increased the CBF response to hypoxia.

In contrast to 15 min of sustained hypoxia, 15 min of intermittent hypoxia, without and with propofol, were unable to generate HVD. Because in our studies the level of hypoxia was relatively mild (inspired oxygen concentration 10%), a limited number of hypoxic pulses were applied, and the duration of the pulses was relatively short, we are unable to predict the impact of repeated episodes of deeper, longer, or more frequent periods of hypoxia on \dot{V}_i . Only limited data are available on ventilatory changes during repeated hypoxia. We recently studied the influence of 0.25% sevoflurane on the ventilatory response to four to six 3-min hypoxic episodes (Sp_{O₂} 84%) separated by 2 min of normoxia in humans.³⁰ Hypoxic \dot{V}_i remained constant over time. In this respect, the behavior of sevoflurane is identical to propofol. In anesthetized pigs, repetition of 12 min of deep hypoxia (inspired oxygen concentration, 7%) was associated with cardiorespiratory depression during the second hypoxic episode.³¹ Further animal studies are required to study the interaction of repetitive (deep) hypoxia and anesthetics and hypnotics on \dot{V}_i and hemodynamics.

Influence of Propofol on the Heart Rate Responses to Hypoxia

The heart rate response to acute hypoxia depends on the effects of hypoxia at various sites in the body. Decreased heart rate may result from a direct effect of hypoxia on the sinoatrial node or hypoxic stimulation of the carotid bodies resulting in stimulation of the vagal centers in the medulla; increased heart rate may result from activation of aortic chemoreceptors, lung receptors (stimulated *via* an increase in \dot{V}_i), or sites within the central nervous system. These factors interact in a complex fashion.³¹ In normal breathing subjects, mild to moderate hypoxia is generally associated with tachycar-

dia. Bradycardia is often observed if hypoxia coincides with apnea or at deeper levels of hypoxia.^{32,33}

In both control and propofol studies, the peak heart rate response to hypoxia occurred 6 min after the initiation of hypoxia (fig. 2). The reason for the relatively slow dynamics of the heart rate response (compared with the \dot{V}_i response) is unknown but may be related to the complex interaction of the various components responsible for the heart rate response, all with their own dynamics. The results of our study give little evidence for an important role of GABA-mediated hypoxic depression of centers in the brain stem involved in heart rate control. In contrast to the \dot{V}_i data, propofol did not enhance heart rate decline during sustained hypoxia or increase depression of the heart rate response to a hypoxic episode after 15 min of hypoxia. Furthermore, the decline of heart rate responses in period H₂ or H₃ (compared with period H₁ + 3 min) may be caused by the decrease in \dot{V}_i . Further studies are needed (for example a protocol that allows for a fixed \dot{V}_i level) to elucidate the mechanism by which propofol affects heart rate responses to hypoxia.

It is not appropriate to simply extrapolate our data (obtained in healthy young male subjects, using imposed isohypercapnic hypoxic stimuli [mean Sp_{O₂}, 86%], without the occurrence of obstructive apnea) to patients under monitored anesthesia care. Studies in patients with sleep apnea indicate that if hypoxia is related to obstructive apnea, initial bradycardia is followed, upon the relief of apnea, by brisk tachycardic responses.^{34,35} In light of the clinical importance of this issue,³⁶ further studies are warranted to examine the influence of sedatives and analgesics on the chronotropic response to hypoxia, especially if upper-airway obstruction is involved.

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