

## 4 Propofol for monitored anesthesia care: *implications on hypoxic control of cardiorespiratory responses*

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,<sup>168,186</sup> 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.<sup>206</sup> Hypoxia of longer duration causes depression of the respiratory centers in the brain stem.<sup>206,210</sup> 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.<sup>50,67</sup> 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  $\gamma$ -aminobutyric acid (GABA) or adenosine, is thought to play a major role in the development of HVD.<sup>49,50,67,68,124</sup> 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).<sup>50,67</sup>

Recent studies indicate that several general anesthetics, including propofol, interact with or modulate the GABA<sub>A</sub> receptor complex.<sup>51,107,126</sup> At clinical concentrations, propofol enhances GABA-evoked chloride currents and causes direct activation of the receptor in the absence of GABA.<sup>51,107</sup> GABA<sub>A</sub> receptors are thought to be involved in the generation of HVD,<sup>49,50,67,206,210</sup> and hence there may be an important role for propofol in modulating/enhancing HVD.

Clinically, hypoxia is often episodic or periodic, especially during sleep or sedation.<sup>162,186</sup> 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 (HR) responses and the bispectral index (BIS) of the electroencephalogram (EEG). The BIS will inform 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.

## METHODS

### *Subjects and Apparatus*

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 a history 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 vein (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 placed and the experiments started.

See METHODS section *Apparatus* of *Chapter 2* for a description of the procedure and apparatus. The EEG and electromyogram were recorded using an Aspect (Natick, MA) A-2000 EEG monitor. The monitor computed the bispectral index (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, (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, (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 set,<sup>34</sup> 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  $\mu$ g/ml and was kept constant during both propofol hypoxic studies. After BIS values had reached a steady level, but at least twenty minutes 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.<sup>207</sup>

### *Data Analysis*

**Sustained Hypoxic Test.** Mean values of the breath-to-breath data were chosen over identical time segments (see figure 1). Period N is the 1-min period before the 15-min of hypoxia; period  $H_1$  the 3<sup>rd</sup> min of hypoxia; period  $H_2$  the 15<sup>th</sup> min of hypoxia; and period  $H_3$  the 3<sup>rd</sup> min of the second hypoxic bout. Differences in  $\dot{V}_i$  between Periods N and  $H_1$  were defined as the first AHR ( $AHR_1$ ), between Periods N and  $H_2$  as the sustained hypoxic response, and between Periods N and  $H_3$  as the second AHR ( $AHR_2$ ). The difference between  $AHR_1$  and sustained hypoxic

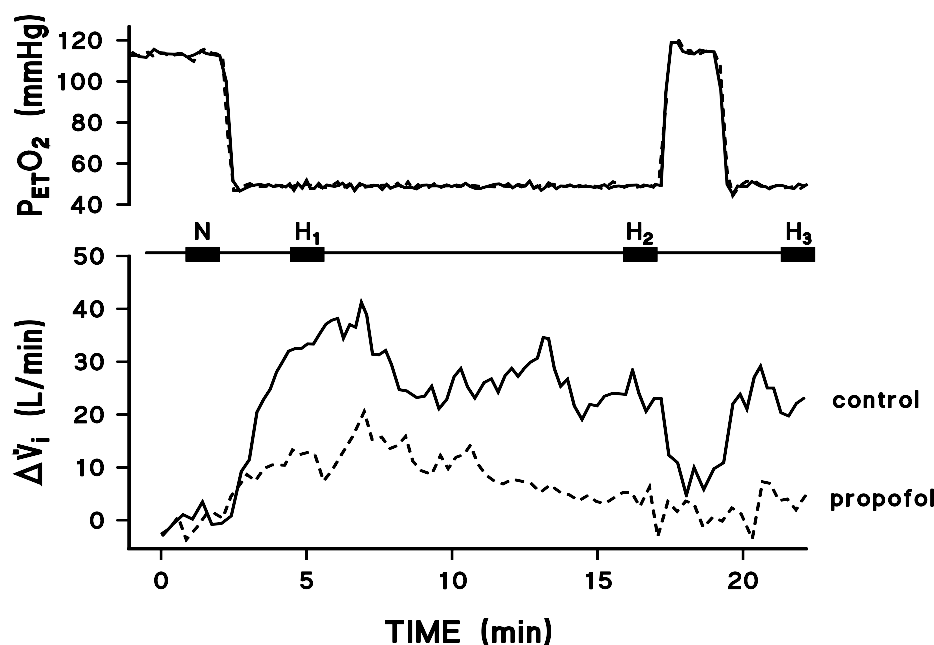


Figure 1. Control and propofol ventilatory responses to the sustained hypoxic test of one subject. *TOP.* End-tidal pressure of oxygen input to the subject. *BOTTOM.* Ventilatory responses above normoxic baseline ( $\dot{V}_i$  data are averaged over six breaths). Period N is the 1-min period before the 15 min of hypoxia; period H<sub>1</sub> min 3 of hypoxia; period H<sub>2</sub> min 15 of hypoxia; and period H<sub>3</sub> min 3 of the second hypoxic bout. Continuous line = control; dashed line = propofol.

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  $S_pO_2$  (unit:  $L \min^{-1} \%^{-1}$ ).

**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 min of normoxia before the first hypoxic pulse (period A) and the third min 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, H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub>) of the sustained hypoxic test. Because peak heart rate responses occurred at period H<sub>1</sub> + 3 min (see Results), for hypoxic HR sensitivities a comparison was made among periods H<sub>1</sub> + 3 min, H<sub>2</sub> and H<sub>3</sub>. 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 pulse. 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 BIS 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  $T_1$ ,  $0.56 \pm 0.23 \mu\text{g/mL}$  at  $T_2$ , and  $0.58 \pm 0.23 \mu\text{g/mL}$  at  $T_3$  (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  $97 \pm 2$  and  $96 \pm 2$  for the sustained hypoxic and hypoxic pulses studies, respectively. During propofol, the mean BIS values were  $76 \pm 14$  for the sustained hypoxic study (range among subjects 53–91; mean coefficient of variation over time = 7%), and  $76 \pm 10$  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 about 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 (figures 1, 2, table 1). Propofol decreased  $\text{AHR}_1$  by 50% from  $1.74 \pm 1.22$  to  $0.89 \pm 0.70 \text{ L min}^{-1} \%^{-1}$  ( $P < 0.001$ ), the sustained hypoxic response by 60% from  $1.11 \pm 0.80$  to  $0.33 \pm 0.30 \text{ L min}^{-1} \%^{-1}$  ( $P = 0.002$ ) and  $\text{AHR}_2$  by 60% from  $1.04 \pm 0.48$  to  $0.39 \pm 0.33 \text{ L min}^{-1} \%^{-1}$  ( $P < 0.001$ ). The absolute magnitude of HVD did not differ between control and propofol ( $0.63 \pm 0.51$  versus  $0.56 \pm 0.52 \text{ L min}^{-1} \%^{-1}$ , not significant). Propofol increased the ratio  $\text{HVD}/\text{AHR}_1$  by more than 50% from  $0.35 \pm 0.16$  to  $0.54 \pm 0.16$  ( $P = 0.02$ ), and caused more depression of the second hypoxic response: The ratio  $\text{AHR}_2/\text{AHR}_1$  was  $0.67 \pm 0.16$  for control and  $0.51 \pm 0.22$  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  $197 \pm 78\%$  and  $200 \pm 63\%$  of baseline, respectively. Corresponding values in the propofol study were  $154 \pm 27\%$  (period B) and  $144 \pm 37\%$  (period C). In control and propofol studies  $\text{AHR}_{\text{first}}$  did not differ from  $\text{AHR}_{\text{last}}$ : control  $1.35 \pm 0.84$  versus  $1.35 \pm 0.67 \text{ L min}^{-1} \%^{-1}$  (not significant; figure 4); propofol  $0.64 \pm 0.39$  versus  $0.58 \pm 0.25 \text{ L min}^{-1} \%^{-1}$  (not significant).

### *Heart Rate Responses*

Because of technical problems, the collection of heart rate data failed in one subject. Propofol decreased normoxic HR by 8–10 beats/min (table 1). In control and propofol sustained hypoxic studies, peak heart rate responses occurred at period  $H_1 + 3 \text{ min}$  (figure 2). Control heart rate sensitivity decreased from its peak by 20% in period  $H_2$  (not significant) and by 35% in period  $H_3$  ( $P < 0.05$ ). Propofol heart rate sensitivity

**Table 1. The Ventilatory, Heart Rate and Bispectral Index Responses to Sustained Hypoxia before and during Propofol Administration**

		Period N	Period H <sub>1</sub>	Period H <sub>2</sub>	Period H <sub>3</sub>
$\dot{V}_i$ (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†
RR (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
$P_{ETCO_2}$ (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
$P_{ETO_2}$ (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*
$S_pO_2$ (%)	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 min before the 15-min hypoxic period; H<sub>1</sub> = min 3 of initial hypoxia;

H<sub>2</sub> = min 15 of initial hypoxia; H<sub>3</sub> = min 3 of the 2<sup>nd</sup> hypoxic episode.

\*  $P < 0.05$  versus Period N. †  $P < 0.05$  versus Period N and H<sub>1</sub>. ‡  $P < 0.05$  versus Period H<sub>1</sub>.

decreased from its peak by 21% in period H<sub>2</sub> ( $P < 0.05$ ) and by 38% in period H<sub>3</sub> ( $P < 0.05$ ). Compared with control, propofol decreased hypoxic heart rate sensitivities in periods H<sub>1</sub> + 3 min, H<sub>2</sub> and H<sub>3</sub> by 27 ± 36%, 36 ± 22 % and 38 ± 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.

## 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 concentration (mean BIS value 76), caused a ~50% reduction of the

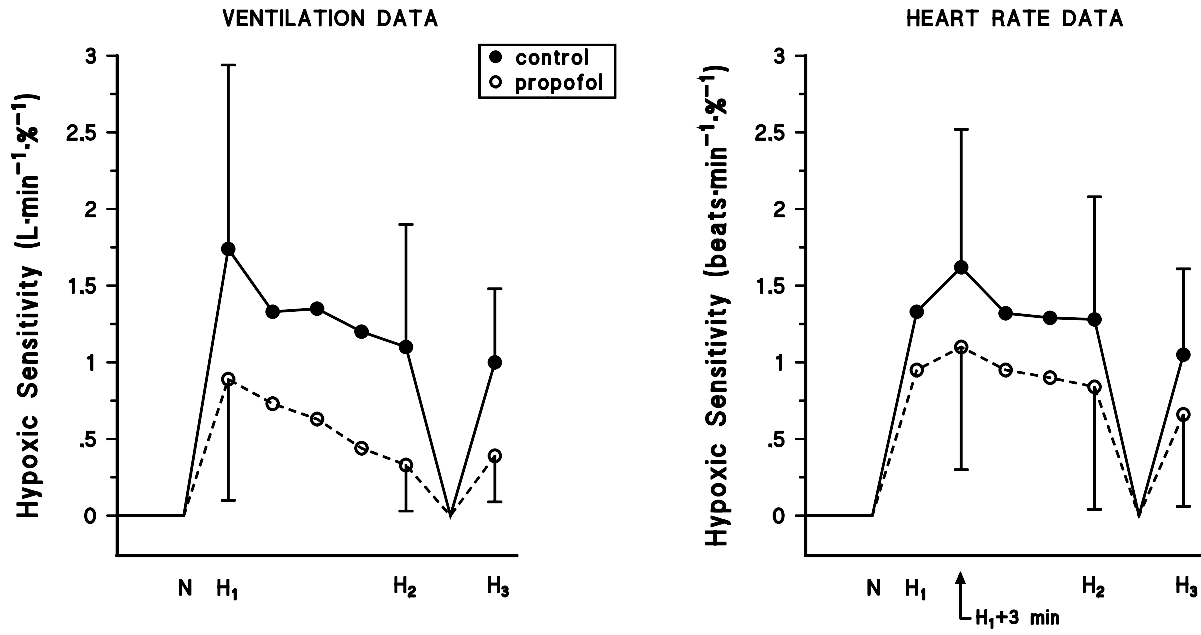


Figure 2. The mean ventilatory (*left*) and heart rate (*right*) responses to the sustained hypoxic test expressed as change in  $\dot{V}_i$  or heart rate per percent in arterial hemoglobin-oxygen saturation ( $S_{pO_2}$ ). For periods N, H<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub> see legend of figure 1. The data points between periods H<sub>1</sub> and H<sub>2</sub> are one minutes averages of minutes 6 (i.e., H<sub>1</sub> + 3 min), 9 and 12 of hypoxia. Values are mean  $\pm$  SD.

ventilatory response to acute hypoxia. Two previous studies examined the influence of propofol on the hypoxic ventilatory response. Blouin *et al.*<sup>20</sup> tested the influence of propofol at a blood concentration of 2  $\mu\text{g}/\text{mL}$  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,<sup>195</sup> their finding is best compared with our observation of propofol-induced reduction of the sustained hypoxic response by about 60%. Nagyova *et al.*<sup>130</sup> showed a reduction of the AHR by 21, 23 and 60% at respective propofol blood concentrations of 0.5, 1 and 2  $\mu\text{g}/\text{mL}$ . This is less than our finding of 50% depression at 0.6  $\mu\text{g}/\text{mL}$ . However, in the study by Nagyova *et al.*'s study, 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.<sup>46</sup>

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 Sadler<sup>151</sup> showed that a high dose propofol infusion (18 to 35 mg/kg per h) into the carotid artery abolished chemorecep-

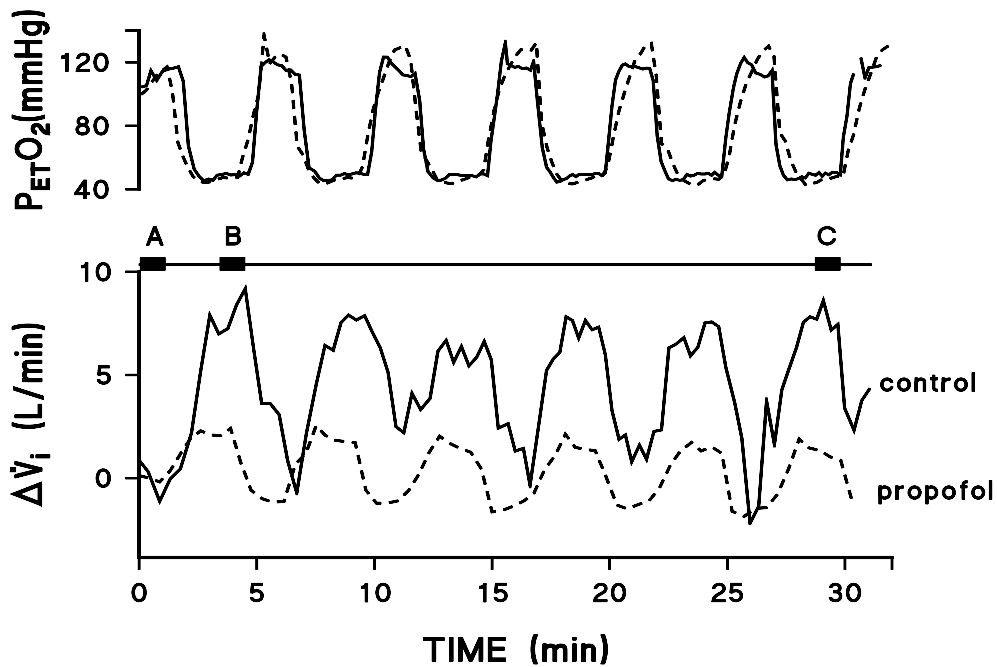


Figure 3. Control and propofol ventilatory responses to intermittent 3-min hypoxic episodes (six hypoxic pulses) of one subject. In between hypoxia there are 2-min normoxic periods. *TOP*. End-tidal pressure of oxygen input to the subject. *BOTTOM*. Ventilatory responses above normoxic baseline ( $\dot{V}_i$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

tor discharge in normoxia and prevented an increase during hypoxia. In humans Dow and Goodman<sup>62</sup> 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.<sup>215</sup> Both sites are involved in respiratory control and may contain central chemoreceptors.<sup>198</sup> 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 gives 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.<sup>185</sup> 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 con-

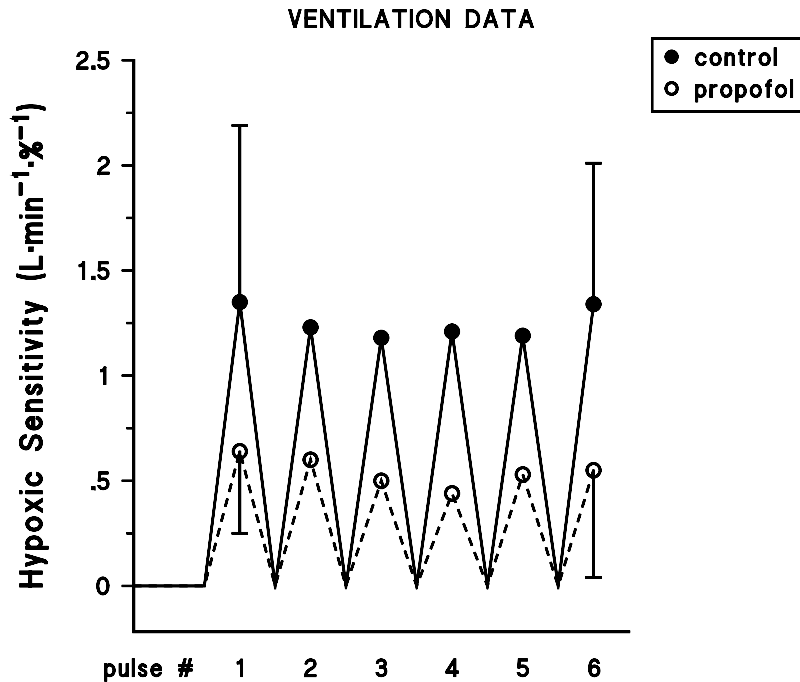


Figure 4. The mean ventilatory responses to hypoxic pulses expressed as change in  $\dot{V}_i$  per percentage in arterial hemoglobin oxygen saturation. Hypoxic duration of each pulse is 3-min. For both control and propofol, the response to the last hypoxic pulses (no. 6) is not different from the response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

trol 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 figure 5], and propofol studies with little to no effect on AHR [open circles in the right part of figure 5]) or sedated or asleep with 50 to 60% depression of AHR (closed circles in the right part of figure 5). In the latter group, variations in the level of sedation or hypnosis (as measured by the BIS) had little further effect on AHR.

#### *Influence of Propofol on Hypoxic Ventilatory Decline*

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).<sup>98</sup> 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 one hour of air breathing is necessary for a full recovery



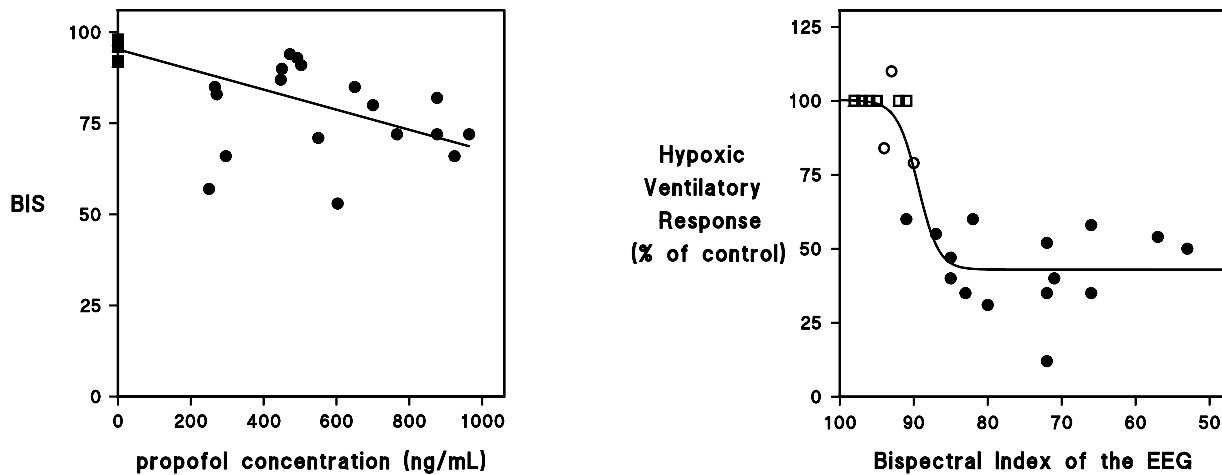


Figure 5. *Left.* The relationship between blood propofol concentration and bispectral index (BIS). Note the twofold larger range in propofol concentration data compared with BIS data. The squares are data points obtained before propofol administration, the circles during propofol infusion. The line 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.

of AHR ( $AHR_2/AHR_1 = 1$ ).<sup>50,67</sup> These observations have led to 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 neurotransmitters candidates are GABA and adenosine.<sup>49,50,67,124,206,210</sup> 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<sub>A</sub> receptor antagonist, reverses HVD in the anesthetized cat.<sup>124</sup>

3. Among and within subjects, the ratio  $HVD/AHR_1$  is constant with changing values of  $AHR_1$ .<sup>50,67</sup> 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.<sup>50</sup>

In our study, propofol did not affect the absolute magnitude of HVD. However, relative to  $AHR_1$ , HVD did increase, causing an increase in ratio  $HVD/AHR_1$ . Furthermore, the ratio  $AHR_2/AHR_1$  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<sub>A</sub> receptors and enhances GABA-ergic transmission.<sup>51,107,145</sup> We therefore suggest that the relative increase in HVD is related to propofol's action at the GABA<sub>A</sub> receptor complex. Other GABA<sub>A</sub> receptor agonists such as midazolam cause similar effects on the ratio  $HVD/AHR_1$ .<sup>49</sup> 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.*<sup>29</sup> showed an increase of the ratio HVD/AHR<sub>1</sub> by the  $\mu$ -receptor agonist alfentanil. Aminophylline, an adenosine-receptor blocker, reduces the ratio HVD/AHR<sub>1</sub>.<sup>68</sup> 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  $PCO_2$ .<sup>73</sup> Although no studies on the influence of propofol on changes in arterial  $PO_2$  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 ( $S_pO_2$  84%) separated by 2 min of normoxia in humans.<sup>175</sup> 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.<sup>115</sup> Further animal studies are required to study the interaction of repetitive (deep) hypoxia and anesthetics/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.<sup>115</sup> In normal breathing subjects, mild to moderate hypoxia is generally associated with tachycardia. Bradycardia is often observed if hypoxia coincides with apnea or at deeper levels of hypoxia.<sup>53,84</sup>

In both control and propofol studies, the peak heart rate response to hypoxia occurred 6 min after the initiation of hypoxia (figure 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 periods  $H_2$  or  $H_3$  (compared with period  $H_1 + 3$  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  $S_pO_2$ , 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.<sup>176,216</sup> In light of the clinical importance of this issue,<sup>161</sup> 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.

