

Evolution of Changes in Upper Airway Collapsibility during Slow Induction of Anesthesia with Propofol

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Background: Upper airway collapsibility is known to increase under anesthesia. This study assessed how this increase in collapsibility evolves during slow Propofol induction and how it relates to anesthesia-induced changes in upper airway muscle activity and conscious state.

Methods: Nine healthy volunteers were studied. Anesthesia was induced with Propofol in a step-wise manner (effect-site concentration steps of $0.5 \mu\text{g} \cdot \text{ml}^{-1}$ from 0 to $3 \mu\text{g} \cdot \text{ml}^{-1}$ and thereafter to $4 \mu\text{g} \cdot \text{ml}^{-1}$ and $6 \mu\text{g} \cdot \text{ml}^{-1}$ [target-controlled infusion]). Airway patency was maintained with continuous positive airway pressure. Pharyngeal collapsibility was assessed at each concentration by measuring critical pressure. Intramuscular genioglossus electromyogram and anesthetic depth (bispectral index score) were monitored throughout. Loss of consciousness was defined as failure to respond to loud verbal command.

Results: Loss of consciousness occurred at varying Propofol effect-site concentrations between 1.5 and $4.0 \mu\text{g} \cdot \text{ml}^{-1}$. Initially genioglossus electromyographic activity was sustained with increases in Propofol concentration, increasing in some individuals. At or approaching loss of consciousness, it decreased, often abruptly, to minimal values with an accompanying increase in critical pressure. In most subjects, bispectral index score decreased a linearly with increasing Propofol concentration with greatest rate of change coinciding with loss of consciousness.

Conclusions: Slow stepwise induction of Propofol anesthesia is associated with an a linear increase in upper airway collapsibility. Disproportionate decreases in genioglossus electromyogram activity and increases in pharyngeal critical closing pressure were observed proximate to loss of consciousness, suggesting that particular vulnerability exists after transition from conscious to unconscious sedation. Such changes may have parallels with upper airway behavior at sleep onset.

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GENERAL anesthesia is associated with relaxation of the upper airways musculature and predisposition to upper airway collapse.^{1–4} Previous studies have indicated that the degree of collapsibility varies with anesthetic depth, but these observations have been made at levels of anesthesia beyond the point at which consciousness is lost, under conditions in which upper airway muscle activity is already profoundly depressed.^{5,6} It is likely that the variation in collapsibility with anesthetic depth that is observed under these circumstances is a consequence of dose-related depression of phasic inspiratory input from respiratory neurons arising from the pontomedullary central pattern generator and of negative pressure reflexes triggered by mechanoreceptors principally situated in the larynx, both of which affect hypoglossal nerve and therefore pharyngeal dilator muscle activity.⁷ A further influence is likely to be a dose-related decrease in end-expiratory lung volume, which decreases longitudinal traction on the upper airway increasing its collapsibility.^{5,8}

However, state of consciousness is another influence on pharyngeal dilator muscle activity and therefore upper airway stability,⁹ and these previous studies have not examined its influence. The purpose of the current study was to determine how upper airway collapsibility changes, and the influence on it of loss of consciousness, during slow stepwise induction of anesthesia with Propofol, a widely used intravenous anesthetic agent with a broad clinical spectrum of action from sedation to anesthesia. In considering its role, we were intrigued by the notion of a bistable thalamocortical switch that determines consciousness or lack of it, which has been proposed as a narcotic mechanism common to both anesthesia and sleep.^{10,11} If such a mechanism existed and if important relative to other determinants of upper airway behavior, we then hypothesized that we would observe an association between loss of consciousness during slow anesthetic induction and changes in upper airway muscle activity and collapsibility, disproportionate to any dose-related changes observed before or after this change in conscious state. We expected that, although the drug level at which such changes occurred would vary between individuals, this pattern of behavior would not. Given their possible common narcotic mechanism, we reasoned that studies of the effect of anesthesia-associated conscious state change on upper airway behavior could inform consideration of the influence of sleep-induced conscious state change on these properties.

Materials and Methods

Subject Selection

Nine volunteers were recruited from staff of the Departments of Anesthesia and Pulmonary Physiology at Sir Charles Gairdner Hospital. Potential vulnerability to upper airway collapse (e.g., obesity, snoring) was not considered at recruitment, with subjects enrolled independent of these considerations. Informed consent was obtained in writing from each subject before participation. The Sir Charles Gairdner Hospital Human Research Ethics Committee (Perth, Western Australia) approved the study.

Subject Preparation

No premedication was administered. Standard monitoring was applied, and a vein was cannulated. Sedation/anesthesia was induced with intravenous Propofol (Diprivan; Astra Zeneca, Alderley Park, Cheshire, United Kingdom) administered *via* a target-controlled infusion system (Alaris Asena PK Syringe Pump; Cardinal Health, Dublin, OH), which calculated effect-site concentration on the basis of a three compartment pharmacokinetic algorithm.¹²

Before drug infusion commencement, intramuscular electrodes were inserted percutaneously to measure genioglossus electromyogram (EMGgg).¹³ Two 25-gauge needles, each containing two sterile 50- μm nylon-coated stainless steel fine-wire electrodes (Stablohm 800B; California Fine Wire Company, Grover Beach, CA), were inserted 1.0 cm from the symphysis menti to a depth of approximately 25 mm. Each needle was inserted approximately 0.3 cm lateral to the midline, angled slightly ventrally towards the mandible to position the recording electrodes close to the origin of the genioglossus. The two pairs of bipolar electromyogram electrodes were referenced to a common ground, placed on the mandible. In addition, a bipolar pair was derived from a single wire from each pair, thereby providing a third electromyogram signal. Each EMGgg signal was amplified, band-pass filtered (10-3000Hz, model 7P3; Grass Instruments, West Warwick, RI) and full-wave rectified and integrated offline (time constant of 100 ms) to yield a moving-time-averaged EMGgg on which later analyses were performed. Immediately after connection of the electromyograms, the subject was asked to perform a series of tongue protrusions and swallows to provide a reference point of maximal activation.

A catheter incorporating a pressure transducer (Gaeltec CTO-4, Dunvegan, Scotland) was passed *via* the external nares into the esophagus such that the transducer was positioned in the mid-esophagus to measure esophageal pressure.⁶

The subject was fitted with a chinstrap, the mouth was taped, and a tight-fitting nasal mask was applied through which oxygen was delivered with a Bain circuit (fresh

gas flow rate of at least 14 l/min). Connected in series to this circuit were an expiratory port and a bilevel positive pressure source (BiPAP; Respironics, Murraysville, PA). This permitted a continuous positive airway pressure (CPAP) to be maintained by using the device's inspiratory positive airway pressure mode. Also, airway pressure could be abruptly reduced to a preset lower level by switching to the ventilator's expiratory positive airway pressure mode on which this level was set.⁶ Alternatively, a preset subatmospheric pressure could be rapidly applied by switching to a regulated vacuum source (model VFC204P; Fuji Electric Co., Tokyo, Japan). Air-flow was monitored with a pneumotachograph (Hewlett Packard 47303A; Waltham, MA) fitted to the nasal mask that had been calibrated with four known flows using flow meters. Nasal mask pressure (P_m) was measured *via* a port in the mask by a pressure transducer (model 143PC; Micro Switch, Honeywell, Morristown, NJ). Before each study, the transducer was calibrated with five known pressures. After the nasal mask had been fitted, the mouth was occluded by adhesive tape, the head was carefully placed in a neutral position (Frankfort plane 90 degrees to horizontal) with lower cervical flexion and upper cervical extension (using a Shea head-rest; Gyrus ENT, Memphis, TN), and a maintenance CPAP level of 10 to 15 cm H_2O was applied to maintain airway patency during anesthetic induction.

Bispectral index score (BIS) monitoring was derived from the frontal electroencephalogram (BIS Quattro[®] Sensor; Aspect Medical Systems, Norwood, MA) and calculated by using the A-2000 BIS[®] monitoring system, software version 3.1 (Aspect Medical Systems).

All signals were digitally recorded continuously at 1000 Hz on a PowerLab data acquisition and analysis system (model 16s, ADInstruments, Sydney, Australia).

Protocol for Assessment of Upper Airway Function during Induction of General Anesthesia

After baseline data were collected Propofol effect site concentration was increased in a stepwise manner to the following levels: 0.5 $\mu\text{g} \cdot \text{ml}^{-1}$, 1.0 $\mu\text{g} \cdot \text{ml}^{-1}$, 1.5 $\mu\text{g} \cdot \text{ml}^{-1}$, 2.0 $\mu\text{g} \cdot \text{ml}^{-1}$, 2.5 $\mu\text{g} \cdot \text{ml}^{-1}$, 3.0 $\mu\text{g} \cdot \text{ml}^{-1}$, 4.0 $\mu\text{g} \cdot \text{ml}^{-1}$, and 6.0 $\mu\text{g} \cdot \text{ml}^{-1}$. When each level was achieved, at least 2 additional minutes were allowed for equilibration and, where necessary, to adjust the level of CPAP to abolish flow limitation. Conscious state was assessed at each level by response to repeated loud verbal command. Unequivocal loss of consciousness was defined as a persistent failure to respond to these commands. At each level, airway pressure was rapidly changed (during early-expiration) from the maintenance level to a lower pressure for five successive breaths before being changed back to the maintenance level (immediately after the fifth inspiratory effort).^{5,6,14-16} After a recovery period, this "pressure drop" procedure was repeated over a range of positive and, where necessary, negative airway pressures to produce variable degrees

of inspiratory flow limitation including airway obstruction. The order of application of pressures was randomized. A maximum negative pressure of -20 cm H₂O was used; if airflow limitation was not observed at this level, then the airway was deemed highly resistant to collapse. After a sufficient number of measurements had been obtained, effect site concentration was increased to the next level. The experiment was complete when satisfactory measurements were obtained at an effect-site concentration of $6.0 \mu\text{g} \cdot \text{ml}^{-1}$ with the infusion then ceased, allowing spontaneous recovery. Monitoring ceased with return of consciousness. Electromyogram electrodes were removed, and careful note was taken of their depth to determine whether any displacement had occurred; none was noted.

Data Collection and Analysis

At each level of anesthesia, upper airway pressure-flow relationships were derived as previously described for sleeping and anesthetized subjects.^{5,6,14-16} Briefly, with each reduction in Pm the inspiratory flow (Vi) profile was examined for each of the five consecutive breaths. When Vi reached a maximum level (V_{imax}) and plateaued as esophageal pressure continued to decrease, flow limitation was considered to be present.⁶ For these flow-limited breaths maximum inspiratory flow (V_{i,max}) and Pm were averaged over breaths 3 to 5 of each sequence at each of the three levels of anesthesia. The relationship between V_{i,max} and Pm was examined and the least squares linear regression equation computed at each level of anesthesia. The regression equation was then solved for pharyngeal critical closing pressure (Pcrit) (the Pm at which V_{i,max} became zero). Measurements of peak inspiratory and expiratory amplitudes of the moving-time-averaged EMGgg signal, relative to electrical zero, were obtained during pressure drop sequences associated with the greatest degree of flow limitation (penultimate to the cessation of flow) at each Propofol concentration. Of the available electrode pairs (see Methods) the pair with most optimal signal to noise ratio was chosen for analysis throughout the study. Tonic activity was defined as the difference between electrical zero and end-expiratory activity. Phasic activity was defined as the difference between end-expiratory and peak-inspiratory activity. Phasic EMGgg amplitude was expressed as a percentage of the maximum value observed during any of the pressure drop sequences used to define Pcrit during the study of each subject. A corresponding BIS value was derived for each Propofol effect site concentration by averaging data over the complete series of pressure drop sequences and intervening recovery periods at that concentration.

Statistical Analysis

The relationship between BIS values and Propofol effect site concentration for each individual was fitted with a logistic sigmoid function (of the form BIS =

$1/(1 + e^{-t})$ where t is a linear function of Propofol concentration). Adequacy of fit of the data were determined by assessment of the coefficient of determination (r^2). The inflection point of the curve fit, the point at which BIS values decreased most rapidly relative to increasing Propofol concentrations, was derived for each subject.

Pearson's correlation coefficients (r) were calculated to determine the strength of the association between the Propofol concentrations at: (i) the inflection point and the point at which loss of consciousness was first noted; (ii) the points of abrupt decrease in phasic EMGgg and loss of consciousness; (iii) the points of increase in Pcrit to a less negative value than -20 cm H₂O and loss of consciousness; and (iv) the points of abrupt decrease in phasic EMGgg and increase in Pcrit to a less negative value than -20 cm H₂O.

The agreement between Propofol concentrations at these points was further assessed by Bland-Altman analyses to determine the mean differences in concentrations (bias), the 95% confidence intervals for the biases and their limits of agreement.

For all analyses a P value less than 0.05 was considered statistically significant.

Results

A total of 9 healthy subjects (6 male and 3 female, age 40 ± 12 (mean \pm SD) yrs, body mass index 23.3 ± 1.9) participated in the study. Measurements of upper airway collapsibility, EMGgg and BIS were obtained in all subjects at Propofol effect site concentrations of 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 $\mu\text{g} \cdot \text{ml}^{-1}$ and, in all but one, at 6.0 $\mu\text{g} \cdot \text{ml}^{-1}$.

For the group, a Pm of 12 ± 1 cm H₂O was sufficient to maintain airway patency and abolish inspiratory flow limitation at each level of anesthesia.

Conscious State

The Propofol effect site concentration at which unequivocal loss of consciousness was first present varied between individuals, ranging from 1.5 to 4 $\mu\text{g} \cdot \text{ml}^{-1}$ (fig. 1, table 1) At Propofol concentrations less than those associated with loss of consciousness, sedation was observed in all subjects and behavioral disinhibition exhibited by several. The Propofol concentrations at which consciousness was lost corresponded to a relatively narrow range of BIS values, between 71 (subject 2) and 53 (subject 3) (fig. 1, table 2). These Propofol levels closely corresponded to the inflection point in the logistic sigmoid curve fitted to the relationship between BIS values and Propofol effect site concentrations for each subject ($r = 0.91$, $P < 0.001$; fig. 2A); the inflection point indicates where BIS values decrease most rapidly relative to increasing Propofol concentrations. The adequacy of fit of the data to the curve function was good, with a range of coefficients of determination (r^2) from 0.89 to

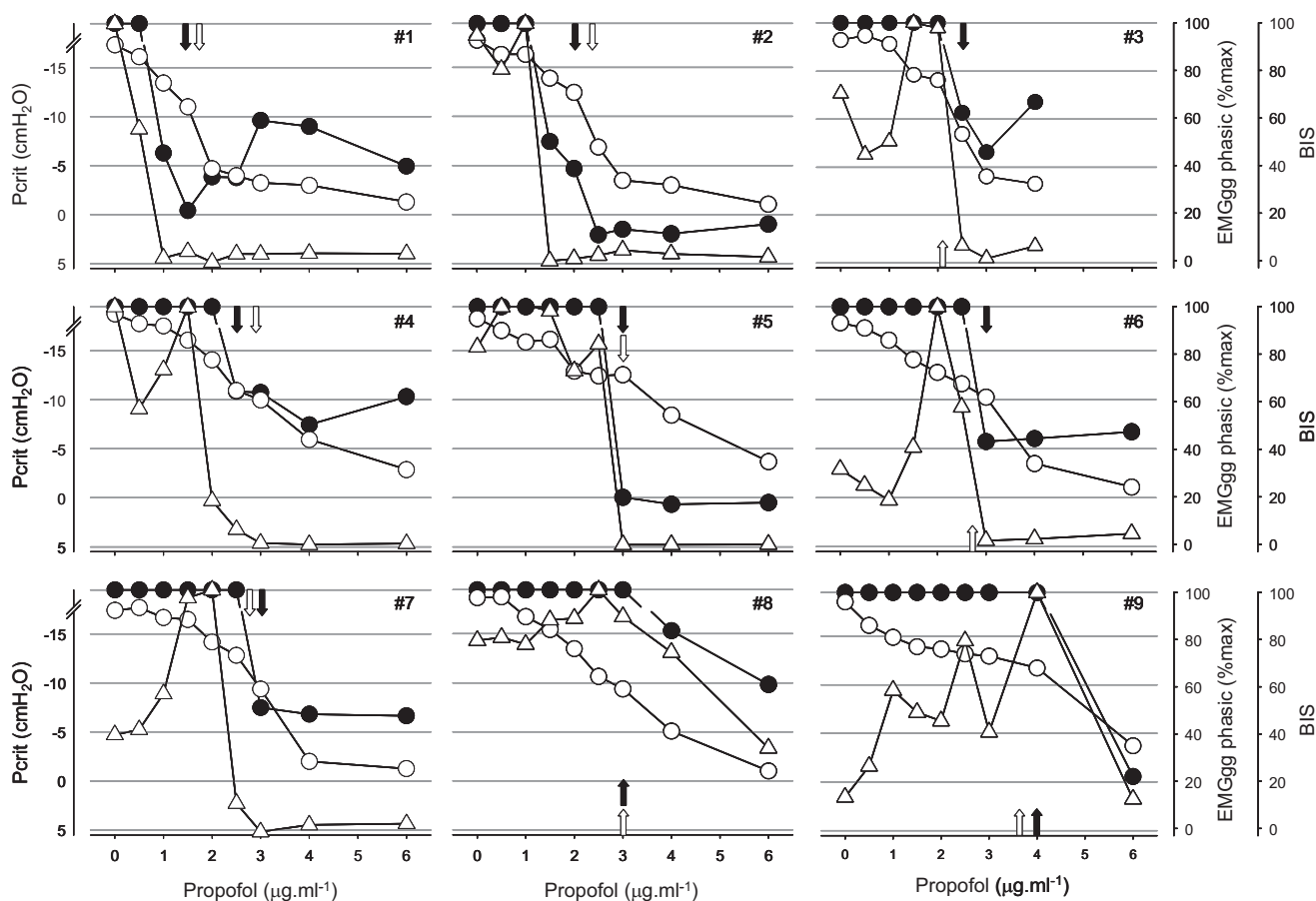


Fig. 1. Relationships among pharyngeal critical closing pressure (Pcrit, cm H₂O; closed circles), phasic genioglossus electromyogram (EMGgg) recorded at Pcrit (% of maximum value recorded in each subject over the series of measurements; triangles), bispectral index score (BIS; open circles), and Propofol effect site concentration ($\mu\text{g}\cdot\text{ml}^{-1}$) in each of the nine subjects. Subjects are presented in order of their susceptibility to upper airway collapse with increasing Propofol levels. Closed arrows = Propofol dose at which unequivocal loss of consciousness was first noted; open arrows = BIS:Propofol inflection point.

0.99 (mean \pm SD = 0.95 \pm 0.04), consistent with the alinear BIS:Propofol relationship evident in most subjects (fig. 1). Bland-Altman analyses (table 3) showed that the bias between Propofol concentrations at loss of consciousness and the BIS inflection point was near zero with close limits of agreement (table 3).

Neuromuscular Activity

Increases in Propofol effect site concentrations were associated with an initial maintenance, and increase in some cases, in phasic EMGgg levels (measured during the pressure drops used to evaluate Pcrit) followed by a decrease, which was usually abrupt. Peak phasic EMGgg levels were observed before or at the point of loss of consciousness. Beyond loss of consciousness, EMGgg decreased to a low proportion of these maximum levels (fig. 1). Although the decrease was observed over a wide range of individual Propofol concentrations (table 1), the concentrations at which EMGgg decreased to below 20% of its maximum value (or to its minimum value in the case of subject 8) in each individual were linearly related to the concentrations at which loss of consciousness was first noted ($r = 0.82$, $P < 0.005$) (fig. 2B).

In 7 of the 9 subjects, phasic EMGgg activity ultimately decreased to less than 5% of the maximum value recorded during the series of pressure drop sequences used to define Pcrit. One subject (subject 8, fig. 1) demonstrated relatively well-sustained phasic EMGgg activity with a late decline; he also had a sustained highly negative Pcrit, indicating an airway that was exceptionally resistant to collapse. The other subject in whom phasic EMGgg remained greater than 5% (subject 9) was the most resistant to the sedative/anesthetic actions of Propofol with a delayed loss of consciousness and decline in BIS relative to the other subjects.

Bland-Altman analysis (table 3) demonstrated that the bias between Propofol concentration at loss of consciousness and reduction in EMGgg to less than 20% of its maximum value was $-0.39 \mu\text{g}\cdot\text{ml}^{-1}$, although the limits of agreement were wide, reflecting the behavior of subjects 8 and 9.

Airway Collapsibility

When the individual Propofol concentrations at which increases in Pcrit to a less negative value than $-20 \text{ cm H}_2\text{O}$ first occurred were related to those at which unequivocal

Table 1. Propofol Effect Site Concentrations at Related Points during Anesthetic Induction

Subject	Propofol Effect Site Concentration ($\mu\text{g} \cdot \text{ml}^{-1}$) at			
	Loss of Consciousness	BIS Inflection Point	EMGgg < 20% Maximum	Pcrit > -20 cm H ₂ O
1	1.5	1.7	1.0	1.0
2	2	2.4	1.5	1.5
3	2.5	2.1	2.5	2.5
4	2.5	2.9	2.0	2.5
5	3.0	3.0	3.0	3.0
6	3.0	2.8	3.0	3.0
7	3.0	2.8	2.5	3.0
8	3.0	3.0	6.0	4.0
9	4.0	3.6	6.0	6.0
Mean \pm SD	2.7 \pm 0.7	2.7 \pm 0.6	3.1 \pm 1.8	2.9 \pm 1.4

Propofol effect site concentrations ($\mu\text{g} \cdot \text{ml}^{-1}$) associated with loss of consciousness, inflection point in the BIS:Propofol relationship, decline in EMGgg to less than 20% of its maximum value (or to its minimum value in case of subject 8), and earliest increase in Pcrit to less negative values than -20 cm H₂O. BIS = bispectral index score; EMGgg = genioglossus electromyogram; Pcrit = pharyngeal critical pressure.

loss of consciousness was first noted (fig. 1, table 1) a close linear relationship was also observed ($r = 0.95, P < 0.001$; fig. 2C). The least negative Pcrit values were observed either at loss of consciousness or the next Propofol increment after it in all subjects, except in subject 8, where EMGgg remained relatively high (greater than 20% of maximum value) even at the maximum Propofol concentration used in the study. Bland-Altman analysis (table 3) demonstrated that the bias between Propofol concentrations at loss of consciousness and those where Pcrit first became less negative than -20 cm H₂O was $-0.22 \mu\text{g} \cdot \text{ml}^{-1}$, with moderate limits of agreement.

The increase in Pcrit was accompanied by a decrease in phasic EMGgg. Pcrit only became less negative than -20 cm H₂O (which was the most negative pressure applied to the upper airway) beyond attainment of peak EMGgg, reaching its least negative values where EMGgg was low (fig. 1). Although these changes were observed over a wide range of Propofol effect site concentrations (table 1), there was a close linear relationship between the Propofol concentrations at which individual decreases in EMGgg and increases in Pcrit were observed

Table 2. Average Bispectral Index Score (BIS) Values at the Lowest Propofol Effect Site Concentration Associated with Loss of Consciousness

Subject	BIS
1	65
2	71
3	53
4	65
5	71
6	62
7	58
8	58
9	68

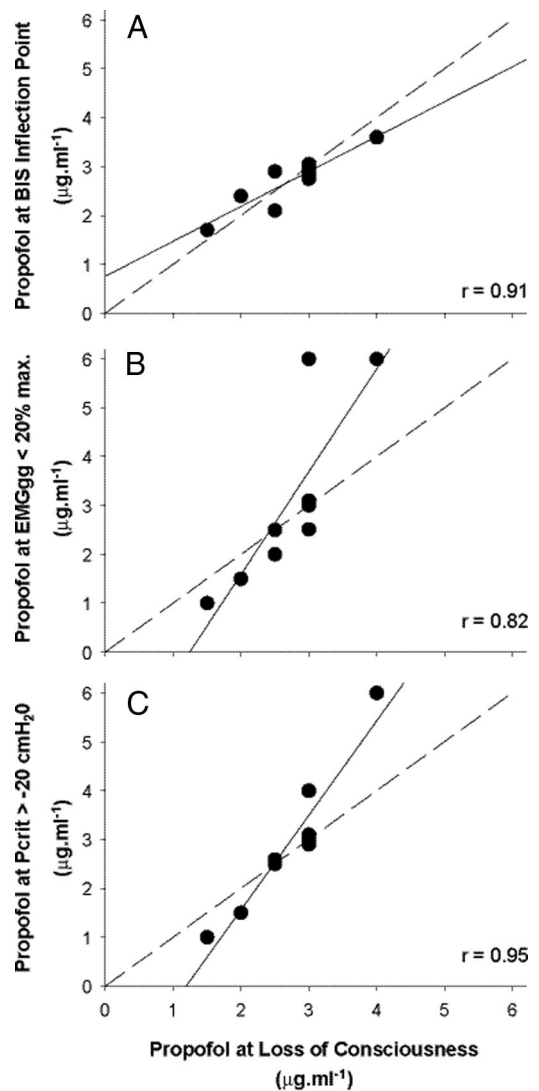


Fig. 2. Propofol effect site concentration ($\mu\text{g} \cdot \text{ml}^{-1}$) at loss of consciousness related to Propofol effect site concentrations ($\mu\text{g} \cdot \text{ml}^{-1}$) at (A) the inflection point of the bispectral index score (BIS):Propofol relationship, (B) a decrease in phasic genioglossus electromyographic activity (EMGgg) to less than 20% of its maximum value (or to its minimum value in subject 8), and (C) at earliest increase in pharyngeal critical pressure (Pcrit) above -20 cm H₂O. Solid lines = regression lines; dashed lines = lines of identity.

($r = 0.92, P < 0.001$) (fig. 3). Subject 8, the subject in whom phasic EMGgg was relatively sustained at higher Propofol levels, exhibited least increase in Pcrit. Bland-Altman analysis (table 3) demonstrated that the bias between the Propofol concentrations at which EMGgg first became less than 20% of its peak value and at which Pcrit was first noted to be less negative than -20 cm H₂O was $0.17 \mu\text{g} \cdot \text{ml}^{-1}$, with moderate limits of agreement.

Discussion

There were five major findings of this study. (1) Although there was significant individual variation in the Propofol effect site concentration at which unequivocal

Table 3. Bland-Altman Analyses of the Agreement Between Propofol Effect Site Concentrations at Related Points during Anesthetic Induction

Comparison	Bias ($\mu\text{g} \cdot \text{ml}^{-1}$)	95% Confidence Interval for Bias ($\mu\text{g} \cdot \text{ml}^{-1}$)	Limits of Agreement ($\mu\text{g} \cdot \text{ml}^{-1}$)
Loss of consciousness vs. BIS inflection point	-0.02	-0.26 to 0.21	-0.62 to 0.58
Loss of consciousness vs. EMGgg < 20% max	-0.39	-1.35 to 0.57	-2.83 to 2.05
Loss of consciousness vs. Pcrit > -20 cm H ₂ O	-0.22	-0.83 to 0.39	-1.78 to 1.34
EMGgg < 20% max vs. Pcrit > -20 cm H ₂ O	0.17	-0.38 to 0.71	-1.22 to 1.55

Bland-Altman analyses showing the agreement between Propofol effect site concentrations ($\mu\text{g} \cdot \text{ml}^{-1}$) associated with loss of consciousness and inflection point in the BIS:Propofol relationship, loss of consciousness and decline in EMGgg to less than 20% of its maximum value (or to its minimum value in case of subject 8), loss of consciousness and earliest increase in Pcrit to less negative values than -20 cm H₂O, and decrease in EMGgg to less than 20% of its maximum value (or to its minimum value in case of subject 8) and earliest increase in Pcrit to less negative values than -20 cm H₂O. n = 9 subjects for each analysis. BIS = bispectral index score; EMGgg = genioglossus electromyogram; Pcrit = pharyngeal critical pressure.

loss of consciousness was observed, this occurred in a relatively narrow range of BIS values. (2) Loss of consciousness coincided with an accelerated decline in BIS values relative to increasing Propofol concentrations. (3) In the lower range of Propofol concentrations, EMGgg activity was sustained, increasing in some individuals. Beyond attainment of its maximum value, at varying individual Propofol concentrations, EMGgg decreased with further concentration increases, often abruptly, to very low levels in most individuals. Peak EMGgg was always observed at or before loss of consciousness. Beyond loss of consciousness, EMGgg activity was relatively low. (4) Pcrit only became less negative than -20 cm H₂O beyond attainment of peak EMGgg, reaching least negative values beyond loss of consciousness, where EMGgg activity was relatively low. (5) The variation between individuals in the Propofol concentrations at which EMGgg activity decreased to low levels and at which Pcrit first became less negative than -20 mmHg reflected the individual variation in Propofol concentrations at which loss of consciousness occurred. Those

most sensitive to the sedating effects of Propofol also demonstrated the earliest depression of EMGgg and earliest increases in Pcrit beyond this level.

This study demonstrates that the progression of effects during slow stepwise induction of anesthesia with Propofol does not occur in smooth continuity but that disproportionate changes in EMGgg activity and upper airway collapsibility occur in a narrow band of Propofol concentrations in each subject. These concentrations differ between individuals in accord with their susceptibility to the drug's sedating effects.

At lower Propofol concentrations, upper airway patency appears relatively well protected with recruitment of the genioglossus muscle (the major pharyngeal dilator), as pharyngeal intraluminal pressures are reduced and an associated highly negative pharyngeal critical pressure, indicating an airway that is highly resistant to collapse. In some cases, EMGgg appeared to increase during conscious sedation relative to wakefulness, raising the possibility of drug-induced disinhibition of muscle activity (discussed below). A decrease in phasic EMGgg activity and increase in Pcrit occurred at or approaching loss of consciousness such that phasic EMGgg activity beyond loss of consciousness was consistently depressed with an accompanying increase in Pcrit, indicating increased pharyngeal collapsibility.

The alinearity of these changes with increasing Propofol concentrations along with the accelerated decrease in BIS values and their collocation is consistent with the notion of a central nervous system "wakefulness stimulus" to upper airway muscles that is lost at or near the point at which there was a loss of response to verbal commands (used here to define loss of consciousness). The notion of a thalamocortical switch has been proposed as a mechanism that determines transitions between wakefulness and sleep and which has also been proposed as a narcotic mechanism in anesthesia.^{10,11} The abruptness of some of the changes observed in EMGgg activity and collapsibility is suggestive of switch-like threshold behavior, although this was not clearly evident in all individuals, suggesting that, if a factor, it was likely to be a component of a multifactorial effect of

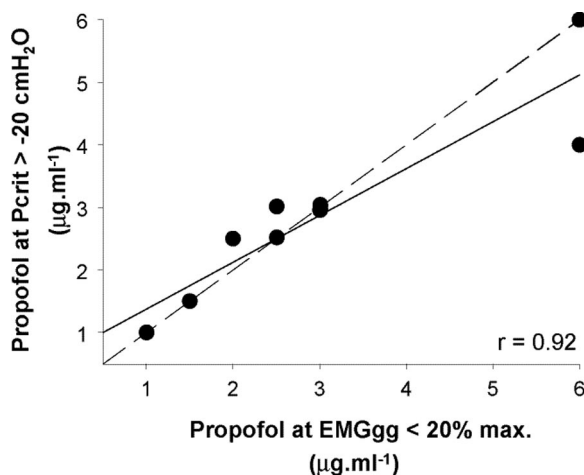


Fig. 3. Propofol effect site concentration ($\mu\text{g} \cdot \text{ml}^{-1}$) associated with a decrease in phasic genioglossus electromyographic activity (EMGgg) to less than 20% of its maximum value (or to its minimum value in subject 8) related to Propofol effect site concentration ($\mu\text{g} \cdot \text{ml}^{-1}$) at the earliest increase in pharyngeal critical pressure (Pcrit) above -20 cm H₂O. *Solid line* = regression line; *dashed line* = line of identity.

anesthetic induction, reflecting the complexity of the neural networks involved and the multiple potential sites of action of the anesthetic ligand.

There were wide interindividual variations in the Propofol effect site concentrations at which loss of consciousness and the attendant upper airway changes occurred, reflecting differing susceptibilities to its effects. This is evident in figure 1, where the subjects are presented in order of susceptibility to upper airway obstruction with increasing Propofol level; subject 1 demonstrates an early increase in Pcrit and subject 9 a late increase. Notably, however, loss of consciousness occurred within a relatively narrow range of BIS values (table 2).

Slow induction of anesthesia is accompanied by a progression of effect from hypnosis and mild disinhibition to sedation to loss of consciousness/rousability to surgical anesthesia. This is reflected, among other things, by a progressive decline in BIS, an indicator of anesthetic depth that is based on analysis of electroencephalogram frequency content, interfrequency phase coupling, and burst suppression.¹⁷ A BIS value of 100 reflects full wakefulness, with explicit memory lost between 90 and 85, heavy sedation associated with scores of 80 to 65, and anesthesia invariably present below 50.^{17,18} Propofol is a convenient drug with which to study these progressive changes because it has a wide clinical spectrum of action from sedation to anesthesia, its effect site concentration can be derived from target-controlled infusion systems based on multicompartment pharmacokinetic modeling,¹² and BIS has been validated with its use.

An important aspect of our methodology was the use of CPAP from the outset to protect upper airway patency throughout the slow, progressive induction process. The effect of this was to avoid the potential for an arousing stimulus from evolving upper airway obstruction (or maneuvers to deal with it) as depth increased, so that the subject was relatively undisturbed by external stimuli as induction progressed. This was not uniformly the case; two of our subjects developed airflow limitation after consciousness was lost while on maintenance levels of CPAP, requiring upward titration of CPAP levels and minor adjustment of head position. This was reflected in some variation in Pcrit levels at levels of Propofol beyond which consciousness was lost in subjects 1 and 3 (fig. 1).

We monitored upper airway muscle activation by examining EMGgg with intramuscular electrodes because the genioglossus is the major pharyngeal dilator muscle. The effect of increasing Propofol levels on conscious state and upper airway collapsibility is reflected in the changes we observed in phasic EMGgg activity during the pressure drops used to determine Pcrit. As Propofol effect site concentration increased, there was an initial increase in activity before loss of consciousness in some

individuals (e.g., subjects 3, 6, 7, 8, 9; fig. 1). The reason for the increase in activity at conscious sedative levels in some individuals is unclear, but it may reflect disinhibition analogous to the behavioral disinhibition that we observed in subjects as Propofol concentration was increased before loss of consciousness. Relevant to this, it is notable that increased genioglossus respiratory activity has been observed in pentobarbital-sedated rats with withdrawal of suprabulbar inhibitory input to the hypoglossal nucleus offered as a putative mechanism.¹⁹

EMGgg activity decreased at or approaching loss of consciousness such that it was at very low levels beyond loss of consciousness in most subjects. This decrease in activity is consistent with current understanding of the stimulatory influences on the hypoglossal nucleus. Wakefulness has a stimulatory influence on this nucleus, and loss of it with sleep onset is a determinant of the increased upper airway collapsibility that accompanies this state change.^{20,21} Our findings suggest that a parallel exists with anesthesia. Other stimulatory inputs into the hypoglossal nucleus are from upper airway negative pressure reflexes (largely mediated by laryngeal receptors)^{22,23} and from phasic respiratory neuron activity arising from the pontomedullary central pattern generator.²⁴ Lung volume change is a further potential contributor to increased upper airway collapsibility with sleep and anesthesia, as the related decreases in functional residual capacity are associated with a loss of longitudinal traction on the upper airway tending to increase its compliance.^{7,8} Our previous findings in anesthetized humans suggest a small dose-related increase in collapsibility within a range of anesthetic levels of Propofol, beyond loss of consciousness, which are likely to be mediated *via* effects on these mechanisms.⁵ However the changes are small relative to the substantial changes in EMGgg activity and Pcrit occurring during the induction sequence.

We defined loss of consciousness as failure to arouse to loud verbal command, a commonly used definition. We determined the Propofol effect site concentration where this was unequivocally the case, recognizing that, because of the stepwise nature of the increases in Propofol effect site concentration used (minimum steps of $0.5 \mu\text{g} \cdot \text{ml}^{-1}$), the precision of this dose determination was limited. Furthermore, while failure to respond to verbal command is a widely used marker of conscious state it is an imperfect guide, testing rousability to aural stimuli only. These factors could account for some apparent imprecision in alignment of "loss of consciousness" with the EMGgg and Pcrit changes in some subjects. Regardless, unequivocal failure to rouse to loud spoken commands represented a useful clinical marker of increased vulnerability to upper airway collapse; the substantial changes in EMGgg and Pcrit occurred in proximity to this point in all subjects, with those most vulnerable to the sedating effects

of Propofol demonstrating greatest vulnerability to its effects on upper airway collapsibility.

To ensure the safety of our procedures, an airway pressure of -20 cm H₂O was the most negative value used during the Pcrit estimates. Changes in upper airway collapsibility at pressures more negative than -20 cm H₂O could not be determined. A disadvantage of this is the limitation it placed on determining where, with increasing Propofol concentrations, an increase in collapsibility might first have occurred. However, if the step-by-step changes in collapsibility are examined in reverse (backward) order of Propofol concentrations from the highest concentrations used towards the lowest, a substantial decrease in collapsibility (= more negative Pcrit) can be observed between the concentrations immediately above and those at the point at which Pcrit first decreases to less than -20 cm H₂O. The negative change in Pcrit at this step is disproportionately large relative to any other step-by-step changes at higher concentrations. An exception to this pattern of response was subject 8, in whom Pcrit values were more negative (and EMGgg activity sustained to a greater degree) than in the other subjects. For the other subjects, these observations suggest a significant change in behavior at this step in the induction sequence, particularly given that our use of a minimum airway pressure of -20 cm H₂O would have acted to limit the magnitude of the Pcrit step change, which may have proved to be greater had lower minimum airway pressures been used.

Parallels between Anesthesia and Sleep

Pharyngeal collapsibility during anesthesia and sleep are related, with Pcrit measured during anesthesia reflecting vulnerability to obstruction during sleep, quantified by the apnea-hypopnea index.²⁵ The behavior observed during anesthetic induction with reduction in EMGgg activity and accompanying increase in collapsibility with increasing Propofol concentrations parallels behavior at sleep onset. In several of our subjects, these changes occurred abruptly, suggesting threshold or switch-like behavior. It has been proposed that a thalamo-cortical switch determines consciousness in both states.^{10,11} It is thought that this consciousness-determining mechanism derives from a reciprocal interaction between sleep- and wake-promoting regions in or adjacent to the thalamus that produce a bistable flip-flop switch controlling the transmission of sensory information through the thalamus to the cortex. Key centers include the inhibitory ventrolateral preoptic nucleus, which is active in and necessary for normal sleep, and the stimulatory posterior lateral hypothalamus, activity from which is necessary for normal wakefulness. The ventrolateral preoptic nucleus is heavily populated with the γ -aminobutyric acid type A-ergic and glycine-ergic

receptors and is a target for the many anesthetic drugs (including Propofol) that readily activate them.²⁶ Although the switch, once activated, can be readily reversed with arousal or awakening from sleep, emergence from anesthesia requires elimination of these drugs. Such switch-like behavior could also explain the relatively abrupt return of consciousness frequently observed during emergence from anesthesia.²⁷ However, as noted earlier, not all subjects exhibited abrupt and contemporaneous changes in all the parameters of interest (EMGgg, Pcrit, BIS, and conscious state), which is perhaps not surprising given the complexity of the neural networks involved and the multiple potential sites of anesthetic action within the central nervous system.

Implications for Procedural Sedation

These common considerations between sleep and anesthesia suggest that upper airway behavior under drug-induced sedation may be a useful guide to its behavior during sleep, providing that sedation is heavy enough to render the subject unconscious. "Sleep nasendoscopy" (nasendoscopy performed under sedation) is commonly used to simulate the effects of sleep in evaluating a patient for surgery to treat snoring and sleep apnea.²⁸ However, the results of the current study suggest that upper airway behavior will differ depending on whether conscious or unconscious sedation is provided for such procedures. The nature and magnitude of the changes after loss of consciousness imply that unconscious sedation is required if sleep-like electromyographic quiescence and associated upper airway flaccidity are to be simulated.

Apart from their implications for the potential applicability of information obtained during studies under sedation to behavior during sleep, the findings are also relevant to the safety of procedural sedation itself. They demonstrate that transition from conscious sedation to unconscious sedation is associated with a disproportionate increase in risk of upper airway obstruction. Besides the well-understood risks associated with loss of the protective effects of rousability, this risk is also related to a decrease in upper airway muscle activity and associated increase in its collapsibility. Loss of rousability is a waypoint in a continuum of effect of sedative and anesthetic drugs that ranges from hypnosis to sedation to anesthesia, terminating in overdose and respiratory arrest. Crossing this threshold of rousability both increases vulnerability to collapse and decreases protection from its effects, with asphyxiation being the inevitable consequence of unrecognized, untreated upper airway obstruction. It may be that BIS or other anesthetic depth monitoring (including, perhaps, upper airway muscle activity itself) could usefully supplement clinical monitoring during procedural sedation to monitor its depth, hence exposure to these risks.

In summary, slow stepwise induction of Propofol anesthesia is associated with an alinear increase in upper airway collapsibility. Disproportionate decreases in EMG activity with concordant increases in Pcrit were observed proximate to loss of consciousness, suggesting that particular vulnerability exists after transition from conscious to unconscious sedation. Such behavior may have parallels with the changes in upper airway behavior that occur at sleep onset.

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