

Differences between Midazolam and Propofol Sedation on Upper Airway Collapsibility Using Dynamic Negative Airway Pressure

J. Russell Norton, M.D.,* Denham S. Ward, M.D., Ph.D.,† Suzanne Karan, M.D.,* William A. Voter, M.A.,‡ Linda Palmer, R.N.,§ Anna Varlese, B.S.,|| Ori Rackovsky,# Peter Bailey, M.D.**

Background: Upper airway obstruction (UAO) during sedation can often cause clinically significant adverse events. Direct comparison of different drugs' propensities for UAO may improve selection of appropriate sedating agents. The authors used the application of negative airway pressure to determine the pressure that causes UAO in healthy subjects sedated with midazolam or propofol infusions.

Methods: Twenty subjects (12 male and 8 female) completed the study. After achieving equivalent levels of sedation, the subjects' ventilation, end-tidal gases, respiratory inductance plethysmographic signals, and Bispectral Index values were monitored for 5 min. Negative airway pressure was then applied *via* a facemask in steps of 3 cm H₂O from -3 to -18 cm H₂O. UAO was assessed by cessation of inspiratory airflow and asynchrony between abdomen and chest respiratory inductance plethysmographic signals.

Results: Equivalent levels of sedation were achieved with both drugs with average (\pm SD) Bispectral Index levels of 75 \pm 5. Resting ventilation was mildly reduced without any changes in end-tidal pressure of carbon dioxide. There was no difference between the drugs in the negative pressure resulting in UAO. Five female subjects and one male subject with midazolam and four female subjects and one male subject with propofol did not show any UAO even at -18 cm H₂O. Compared with males, female subjects required more negative pressures to cause UAO with midazolam ($P = 0.02$) but not with propofol ($P = 0.1$).

Conclusions: At the mild to moderate level of sedation studied, midazolam and propofol sedation resulted in the same propensity for UAO. In this homogeneous group of healthy subjects, there was a considerable range of negative pressures required to cause UAO. The specific factors responsible for the maintenance of the upper airway during sedation remain to be elucidated.

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* Assistant Professor, ** Professor, Department of Anesthesiology, ‡ Senior Technical Associate, § Clinical Research Associate, || Undergraduate Student, Department of Biomedical Engineering, † Professor, Department of Anesthesiology and Biomedical Engineering, School of Medicine and Dentistry, University of Rochester. # Undergraduate Student, Yeshiva University, New York, New York.

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Address correspondence to Dr. Ward: Department of Anesthesiology, 601 Elmwood Avenue, Box 604, Rochester, New York 14642. denham_ward@urmc.rochester.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

ALTHOUGH it is well known that sedation, like sleep, can result in apnea due to upper airway obstruction (UAO), there are no studies directly comparing two different drugs' propensity to cause UAO. This is in contrast to many studies comparing the depressive effects of sedatives and analgesics on the chemoreflex drive to breathe (see Ward and Temp¹ for a review and further references). Although it can be argued that sedation-induced airway obstruction is more common and more dangerous than hypoventilation, only recently has a quantitative method been used to measure the propensity to cause airway obstruction analogous to the provocative hypercapnic or hypoxic ventilatory responses.² The determination of the airway pressure causing airway collapse or flow limitation in patients with obstructive sleep apnea has been used extensively in sleep apnea research. The application of negative airway pressure to determine the collapsibility of the upper airway, as seen by flow limitation or complete obstruction, has been used during sedation,³ anesthesia,⁴ and partial neuromuscular blockade.⁵

Midazolam and propofol are commonly used for moderate sedation during a variety of medical procedures. Although there are case reports describing respiratory complications with either drug, there are also case series attesting to their safety.⁶ We have designed this study to measure the pressure at which UAO occurs (P_{UAO}) in response to dynamic negative airway pressure (DNAP) in healthy subjects sedated to equal end points with continuous intravenous infusions of either propofol or midazolam. This pressure is similar to the critical airway pressure (P_{crit}) determined by extrapolation and commonly used in sleep apnea studies.⁷ Because clinical sedations are generally performed with supplemental oxygen, we performed the main experiments in mild hyperoxia. However, because hyperoxia may reduce ventilatory drive and increase the tendency for UAO, supplemental experiments were performed in mild hypoxia. In addition, because men have a higher incidence of sleep apnea⁸ than women, although the differences between men and women in upper airway mechanics are controversial,⁹ we planned to compare the responses between men and women. We also measured the response to DNAP during the recovery period for each drug.

Materials and Methods

The study was completed at the University of Rochester Medical Center (Rochester, New York) and approved by the University of Rochester (Rochester, New York) Research Subject Review Board; written informed consent was obtained from all participants. Healthy volunteers, aged 18–50 yr, were asked to fast from midnight before the experiment and to refrain from alcohol- and caffeine-containing beverages for 24 h before the experiment. Exclusion criteria included obesity (body mass index [BMI] > 29 kg/m²); symptoms of sleep apnea or a tendency for airway obstruction (determined by a score > 11 on the Epworth Sleepiness Scale¹⁰ or UAO during a trial breathing run with DNAP challenges while awake); men with beards (inadequate facemask seal); presence of significant smoking, alcohol use, or drug use history; allergy to study medications; and lactation and possible pregnancy in females.

Upon arrival at the laboratory, volunteers lay supine on a stretcher while a pulse oximeter, electrocardiogram, and blood pressure cuff (Siemens Medical Electronics, Danvers, MA) were applied. A 20-gauge intravenous catheter was inserted in a forearm vein for administration of the study drugs, and lactated Ringer's solution was infused at 50 ml/h as the carrier fluid *via* a volumetric infusion pump (Abbott Plum infusion pump; Abbott Laboratories, Abbott Park, IL). Respiratory inductance plethysmography bands (Respitrace System; Ambulatory Monitoring Inc., Ardsley, NY) were placed on the chest wall and abdomen at the positions recommended by the manufacturer. Bispectral Index (BIS) leads were applied to the forehead after skin cleansing with alcohol (BIS[®] Monitor; Aspect Medical Systems, Newton, MA). The subjects were then allowed to relax before the first experimental intervention.

The techniques of respiratory measurements have been described in detail previously.^{3,11} Subjects breathed from a gas-mixing chamber *via* a tight-fitting facemask (Vital Signs, Totowa, NJ). Inhaled and exhaled volumes were measured by digital integration of flow signals derived from a bidirectional pneumotachograph (model 4700B; Hans Rudolph, Kansas City, MO). Airway gases were sampled continuously by a mass spectrometer (MGA 110; Perkin-Elmer, Pomona, CA). Airway pressure in the breathing mask was measured with a variable reluctance diaphragm pressure transducer (Validyne Engineering, Northridge, CA). Computer-driven high-flow (total flow of 60 l/min) stepper-motor valves provided nitrogen, carbon dioxide, and oxygen to the gas-mixing chamber at desired concentrations. The exhaust flow from the chamber to the hospital central vacuum system

was controlled *via* a proportional flow control valve (type 154; MKS Instruments, Wilmington, MA) with integral plus proportional negative feedback from the pressure measured in the chamber. The desired pressure was manually selected, and the servo system maintained this pressure despite the subject's ventilation. Breath-by-breath ventilation (l/min), tidal volume (liters), breathing frequency (breaths/min), end-tidal gas concentrations (P_{ET}O₂ and P_{ET}CO₂, mmHg), and hemoglobin oxygen saturation by pulse oximetry (percent) were determined and collected using the TIDAL software package.††

The order of the study drugs was randomized (*via* a computer-generated random number table) between the 2 experimental days. Each drug was given *via* a computer-controlled infusion until the participant reached a level of mild to moderate sedation defined by a BIS value of 75 and an Observer's Assessment of Alertness/Sedation (OAA/S) score of 2 or 3. The depth of sedation with propofol and midazolam has been validated to be consistently predicted with the BIS and OAA/S for both drugs.^{12,13} The computer drug delivery system involved the use of a laptop computer (HP Omnibook; Hewlett-Packard, Palo Alto, CA) running the STANPUMP computer program‡‡ connected to a syringe infusion pump (model 22; Harvard Apparatus, Holliston, MA). For propofol, the Marsh parameter set¹⁴ was used with an initial target effect site concentration of 1.0 µg/ml. The effect site concentration was increased every 5–10 min by 0.1–0.25 µg/ml until the sedation targets (BIS and OAA/S) were reached. For midazolam, the Albrecht parameter set¹⁵ was used with an initial target effect site concentration target of 100 ng/ml. The effect site concentration was increased by 10–25 ng/ml every 5–10 min until the sedation targets were reached. Only the investigator administering the drug knew its identity. The infusion tubing for the study drug was covered with a sheet and connected to the subject between the intravenous tubing and the intravenous catheter. Subjects were told they might experience some pain on injection with both study drugs. The effect site target concentration remained the same for both the hyperoxic and hypoxic sedation experiments.

The experimental protocol consisted of five breathing runs: awake, sedation during hyperoxia, sedation during hypoxia, and recovery at 15 and 45 min after discontinuation of the study drug infusion. A rest period of at least 15 min was given between breathing runs. The fraction of inspired oxygen was 0.21 for the awake breathing run. End-tidal oxygen was kept at a target of 150 mmHg to mimic the common clinical situation during the first sedation breathing run and was kept at a target of 57 mmHg (mild hypoxia, expected saturation of 85–90%) for the second sedation breathing run. Supplemental oxygen (2 l/m *via* nasal prongs) was given while the participants were being sedated to the desired end point, between the experimental runs, and during recovery.

†† Available at: <http://sourceforge.net/projects/tidal/>. Accessed March 17, 2005.

‡‡ STANPUMP program. Available at: <http://anesthesia.stanford.edu/pkpd>. Accessed July 11, 2005.

ery as needed to prevent hypoxemia. Each breathing run commenced with a 5-min period of resting ventilation during which ventilatory variables were measured. DNAPs of -3 , -6 , -9 , -12 , -15 , and -18 cm H₂O were applied sequentially at end-exhalation, as previously described,³ for approximately five breaths. Ventilation was then allowed to stabilize for 2–5 min before the next DNAP. The airway pressure, pneumotachograph flow signal, and respiratory inductance plethysmography signals were displayed in real time on the computer to monitor the response to the DNAP. If UAO criteria (loss of airflow as shown by the pneumotachograph, and capnograph signals and respiratory inductance plethysmography abdomen and chest wall signals showing phase shifting and obvious asynchrony for at least two consecutive breaths) were met, the DNAP challenges were stopped and the breathing run was terminated.

For the breathing run during hypoxia, two DNAP pressures were used: the pressure that caused UAO, as determined by the online monitoring during the preceding hyperoxia sedation experiment, and a pressure 3 cm H₂O more positive. If no UAO was observed during the hyperoxia sedation, DNAP pressures of -18 and -15 cm H₂O were used. During the hypoxia run, DNAP was applied at 2 and 10 min of hypoxia because of the possible difference in the ventilatory response during early and late hypoxia.¹¹ After meeting routine ambulatory surgery discharge criteria, subjects were escorted home using previously arranged transportation. A follow-up phone call was made 24 h later to check for any possible complications of the protocol. Subjects returned 7–45 days later to repeat the study with the second drug.

Data and Statistical Analysis

Sample size estimation was difficult for this study because it is not known how much difference in P_{UAO} is of clinical significance. Estimates of mean and SD values for P_{UAO} during sedation with midazolam were -8.0 ± 4.0 cm H₂O from data obtained in a previous study in our laboratory.³ We estimated that a sample size of 20–30 subjects would be needed to detect a 3- to 6-cm H₂O difference in P_{UAO}. All statistical analysis was done using Stata (Stata, Inc., College Station, TX). *P* values are given when less than 0.05, the level used for significance.

For the postexperiment analysis, the respiratory variables were calculated by TIDAL as done on-line. In addition, data were analyzed using software written in Matlab (The MathWorks, Inc., Natick, MA) to determine the peak inspiratory flow for each breath during the DNAP periods. This peak flow was calculated relative to the average flow over the whole breath to account for possible leaks around the mask. The respiratory inductance plethysmography data were analyzed by calculating the percent of time the abdomen and rib cage signals

were out of phase during the breath (*i.e.*, when the signals were moving in opposite directions, indicating expansion of the abdomen with contraction of the rib cage or *vice versa*). Unobstructed breathing generally showed an asynchrony percentage of less than 20%. Postexperiment data analysis was performed with blinding to the drug. The criterion for UAO was a peak inspiratory flow of less than 50 ml/s, and the respiratory inductance plethysmography indicated respiratory movements with an asynchrony percentage of greater than 60% for two consecutive breath efforts during a DNAP challenge. The pressure that caused the UAO was designated as the obstructing airway pressure (P_{UAO}).⁷ This method of determining P_{UAO} differs from the determination of the P_{crit} in that the resolution is 3 cm H₂O because we are not interpolating between pressures.⁷ Although this method has a more definite end point (*i.e.*, actual UAO is observed), we potentially could be estimating a more negative P_{UAO}, by as much as 3 cm H₂O, than the P_{crit} obtained when extrapolating. However, because it is unlikely that such a small difference could have clinical significance, we decided to use the more definite end point.

The primary outcome variable was the measurement of the P_{UAO} during the hyperoxia sedation runs. Because the P_{UAO} was measured with an ordinate scale, the distributions were compared between drugs using the Wilcoxon signed-rank test for matched observations. Some participants did not obstruct even at the minimum DNAP of -18 cm H₂O and were therefore given a value of less than -18 cm H₂O in the analysis. Differences between men and women were compared using the Mann-Whitney two-sample statistic. Ordered logit regression analysis on P_{UAO} was used to determine whether there were any cofactors that had significant effects.

Basic breath-by-breath ventilatory variables were averaged over 2 min, ending at approximately 1 min before the first negative-pressure challenge except for the hypoxia runs, where the average was for 1 min, 2.5 min after the start of the hypoxia and approximately 30 s before the first negative-pressure interval. The BIS values during these intervals were also averaged, and the OAA/S scores taken at the start of the runs were recorded. All variables were tested for a drug effect using analysis of variance by drug, sex, and sex nested within subject. Within each drug treatment, a sex effect was tested for using analysis of variance.

During sedation, respiratory arrhythmias occurred before the first negative-pressure provocation in some subjects. These arrhythmias were central, obstructive, or mixed (fig. 1 shows an example of a mixed arrhythmia). We quantified these arrhythmias using the criteria of Wu and Drummond¹⁶ (a substantial increase in inspiratory flow on a single breath and a change in the waveform from rounded to more peaked) during the 5 min before the first DNAP episode. We also required at least two

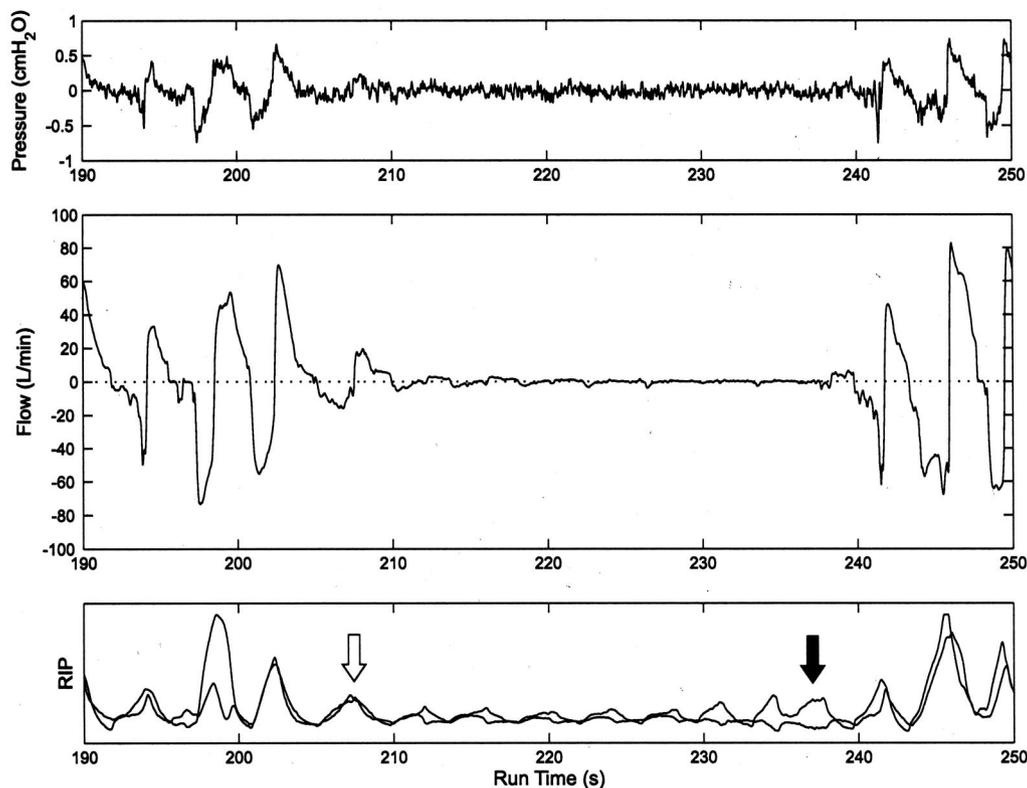


Fig. 1. An example of a respiratory arousal in a sedated subject before the first negative-pressure provocation. The *top graph* shows continuous (sampled at 20 ms and smoothed with a three-sample moving average) airway pressure, the *middle graph* shows the airflow (expiration positive and inspiration negative), and the *bottom graph* shows the abdomen and chest respiratory inductance plethysmography (RIP) signals (relative scale). Note that the episode began with a decrease in ventilation to apnea without any airway obstruction (*open arrow*), while just before the arousal, several obstructed breaths occurred (*shaded arrow*).

breaths to meet the criteria to avoid counting sighs. The distributions were compared between drugs using the Wilcoxon signed-rank test for matched observations. Differences between men and women were compared using the Mann-Whitney two-sample statistic.

Results

Thirty-five subjects were enrolled in the protocol, and 20 subjects completed both experimental days. The other subjects did not complete one or both sessions because of scheduling problems, and 1 subject could not complete the midazolam session because of an inability to cooperate while sedated. Table 1 contains the demographics for the subjects. The subjects tolerated the drug infusions, which were titrated to obtain the desired OAA/S score, without any adverse events. The median

Table 1. Subject Characteristics

	n	Age, yr	BMI, kg/m ²	ESS Score
Female	8	24 ± 7	22.4 ± 2.3	6.1 (2–11)
Male	12	22 ± 5	22.3 ± 1.6	5.7 (0–11)

Values are presented as mean ± SD for age and body mass index (BMI), mean and range for Epworth Sleepiness Scale (ESS) score. An ESS score was not obtained from one male subject.

(range) target effect site concentrations for female and male subjects respectively, were 105 (50–145) and 110 (100–135) ng/ml for midazolam and 1.45 (1–2) and 1.5 (1.2–2.25) µg/ml for propofol. The total drug amounts infused for female and male subjects respectively, were 10.1 ± 2.3 and 10.7 ± 1.7 mg for midazolam and 292 ± 91 and 345 ± 77 mg for propofol. None of these differences was significant at the $P = 0.05$ level.

Table 2 contains average ventilation, P_{ETCO_2} , BIS, and heart rate data before the first negative-pressure period and the OAA/S score obtained just before the start of the breathing run. In the control period, female subjects had a slightly lower ventilation and lower P_{ETCO_2} . During the sedation experiments, ventilation, BIS, OAA/S scores, and heart rate were comparable between drugs and sexes, although female subjects still had a somewhat lower P_{ETCO_2} . Hypoxia caused the expected increase in ventilation. Interestingly, the saturation, BIS, OAA/S score, and heart rate were all lower with propofol than with midazolam. Compared with midazolam, propofol resulted in greater BIS and OAA/S scores and lower P_{ETCO_2} values at 15 and 45 min after the termination of the drug infusions.

Figure 2 shows the determination of P_{UAO} in one subject. The progression from partial to full obstruction is readily seen as the airway pressure is decreased. Figure 3

Table 2. Comparison of Results between Drugs and Subject Sex

	Midazolam			Propofol		
	Female	Male	Both	Female	Male	Both
Control						
Ventilation, l/min	6.0 ± 1.1*	7.3 ± 1.4	6.8 ± 1.4	6.0 ± 0.8*	7.9 ± 1.6	7.2 ± 1.6
PETCO ₂ , mmHg	36 ± 2.5*	41 ± 2.4	39 ± 3.3	36 ± 2.4	39 ± 4.4	38 ± 4.0
BIS	94 ± 6	94 ± 5	94 ± 5	94 ± 5	94 ± 4	94 ± 4
Heart rate, beats/min	68 ± 7	66 ± 9	67 ± 8	69 ± 19	68 ± 10	69 ± 14
Sedation						
Ventilation, l/min	5.2 ± 0.4	6.4 ± 2.0	5.9 ± 1.6	5.4 ± 1.2	5.8 ± 1.2	5.6 ± 1.2
PETCO ₂ , mmHg	36 ± 2.8*	42 ± 4.5	40 ± 4.9	34 ± 2.1*	41 ± 4.6	39 ± 5.3
BIS	74 ± 5	75 ± 6	75 ± 5	78 ± 2	74 ± 6	75 ± 5
OAA/S score	2.7 (2–3)	2.5 (2–3)	2.6 (2–3)	2.7 (2.5–3)*	2.4 (2–3)	2.5 (2–3)
Heart rate, beats/min	69 ± 7	71 ± 7	70 ± 6	71 ± 15	66 ± 7	68 ± 11
Hypoxia						
Ventilation, l/min	9.1 ± 2.1	8.6 ± 2.0	8.8 ± 2.0	8.0 ± 1.8	7.7 ± 2.4	7.8 ± 2.1
PETCO ₂ , mmHg	35 ± 3.1*	42 ± 3.8	40 ± 5.6	35 ± 2.1*	44 ± 4.2	40 ± 5.7
Saturation %	91 ± 3	89 ± 4	90 ± 4	89 ± 4.5	86 ± 3.5	86 ± 4†
BIS	71 ± 12	73 ± 7	72 ± 9	67 ± 6	69 ± 8	68 ± 7†
OAA/S score	2.8 (2–4)	2.5 (2–3)	2.6 (2–4)	2.6 (2–3)	2.2 (1.5–3)	2.3 (1.5–3)†
Heart rate, beats/min	81 ± 14	75 ± 9	77 ± 11	74 ± 13	70 ± 8	72 ± 11†
15-min recovery						
Ventilation, l/min	5.2 ± 0.6*	6.7 ± 1.8	6.1 ± 1.6	5.7 ± 0.8*	7.2 ± 1.6	6.6 ± 1.5
PETCO ₂ , mmHg	36 ± 1.9*	43 ± 3.4	40 ± 4.4	36 ± 3.1*	41 ± 3.3	39 ± 4.1†
BIS	76 ± 5	76 ± 8	76 ± 7	91 ± 7	87 ± 9	88 ± 8†
OAA/S score	3.6 (3–4)	3.1 (2–4)	3.3 (2–4)	4.1 (3.5–5)	4 (3.5–5)	4.1 (3.5–5)†
Heart rate, beats/min	66 ± 8	65 ± 8	65 ± 8	58 ± 15	61 ± 8	60 ± 11†
45-min recovery						
Ventilation, l/min	5.8 ± 0.7	6.9 ± 1.9	6.5 ± 1.6	5.8 ± 0.9	6.5 ± 1.1	6.2 ± 1.0
PETCO ₂ , mmHg	35 ± 3.4*	43 ± 3.7	40 ± 5.2	35 ± 2.0*	40 ± 1.9	38 ± 3.1†
BIS	86 ± 8	79 ± 6	82 ± 7	92 ± 6	91 ± 6	91 ± 6†
OAA/S score	4 (3.5–4.5)	3.4 (3–4)	3.6 (3–4.5)	4.8 (4.5–5)	4.8 (4.5–5)	4.8 (4.5–5)†
Heart rate, beats/min	69 ± 5*	62 ± 7	65 ± 7	64 ± 12	59 ± 7	61 ± 9

Values presented as mean ± SD or mean and range for Observer's Assessment of Alertness/Sedation (OAA/S) scores for the 2 min ending approximately 1 min before the first negative-pressure challenge, except for the hypoxia runs where the average is for 1 min, 2.5 min after the start of hypoxia and approximately 30 s before the first negative-pressure interval. Heart rate data are missing for one male subject (both drugs) for the control and sedation experiments, for one male subject (midazolam) in the 15-min recovery experiment, and one male subject (midazolam) in the 45-min recovery experiment. Bispectral Index (BIS) data are missing for one female subject (midazolam) and one male subject (propofol) in the control experiments, three female subjects (two for propofol and one for midazolam) and one male subject (propofol) in the sedation experiment, and one male subject (midazolam) in the 45-min recovery experiment. The 45-min recovery experiment was not performed in one female subject (midazolam). Heart rate and saturation data are missing from one male subject (midazolam) for the hypoxia runs.

* $P < 0.05$, female different from male within the same drug. † $P < 0.05$, midazolam different from propofol.

PETCO₂ = end-tidal pressure of carbon dioxide.

shows the histograms of the P_{UAO} by drug and by sex. There are 40 subject-drug combinations, 20 subjects for each of the two drugs. Eleven subjects (5 female and 1 male with midazolam and 4 female and 1 male with propofol) did not demonstrate obstruction at any negative pressure and therefore had a P_{UAO} of less than -18 cm H₂O, whereas 15 subject-drug combinations readily saw obstruction and had values of -3 or -6 cm H₂O. There was no difference in P_{UAO} between the two drugs overall ($P = 0.9$) or when grouped by sex. For both drugs combined, female subjects had a statistically significant ($P = 0.004$; fig. 3) more negative P_{UAO} than the male subjects. Grouped by drug, this was significant for midazolam ($P = 0.02$) but not for propofol ($P = 0.1$). Ordered logit regression with P_{UAO} as the independent variable and sex, drug, age, BMI, respiratory arousals (see last paragraph of this section), and sleepiness scores showed only sex as a significant ($P = 0.003$) factor. No

airway obstructions were obtained with DNAP down to -18 cm H₂O for propofol during both recovery periods. However, with midazolam, 5 subjects had P_{UAO} less negative than -18 cm H₂O at the 15-min recovery run, and 3 subjects still showed a P_{UAO} less negative than -18 cm H₂O at the 45-min recovery run.

The protocol for testing airway obstruction during hypoxia required that P_{UAO} be estimated using the data obtained on-line during the sedation experiment. We intended to then apply this pressure and a pressure 3 cm H₂O less negative early in the hypoxic interval (before 5 min of hypoxia) and later in the hypoxic interval (after 10 min of hypoxia). However, because of technical issues in applying the negative pressures at the specified times and because the selected pressures did not always correspond to the P_{UAO} ultimately determined from the off-line analysis, the protocol was not followed exactly in every subject. Because the timing of the negative-pres-

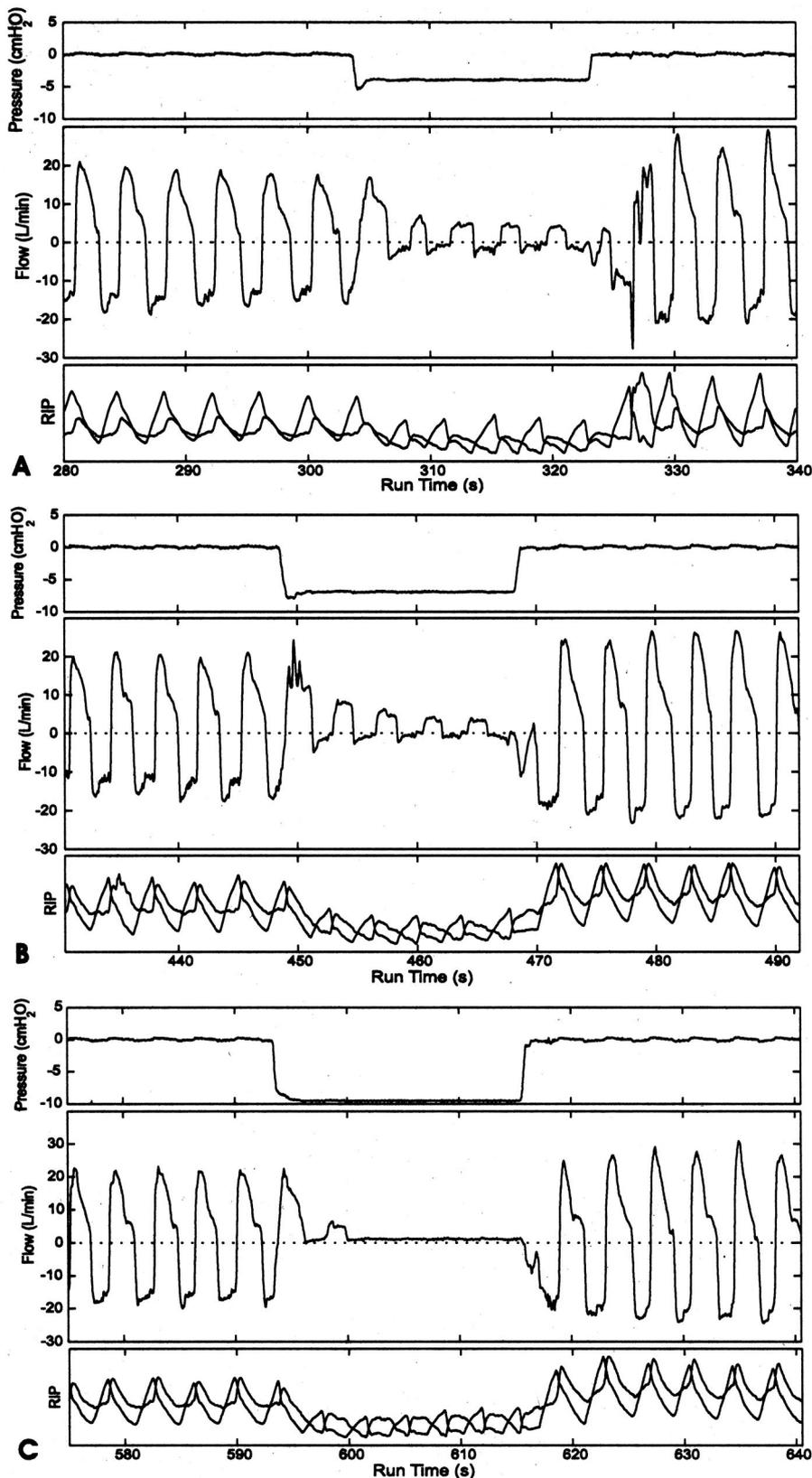
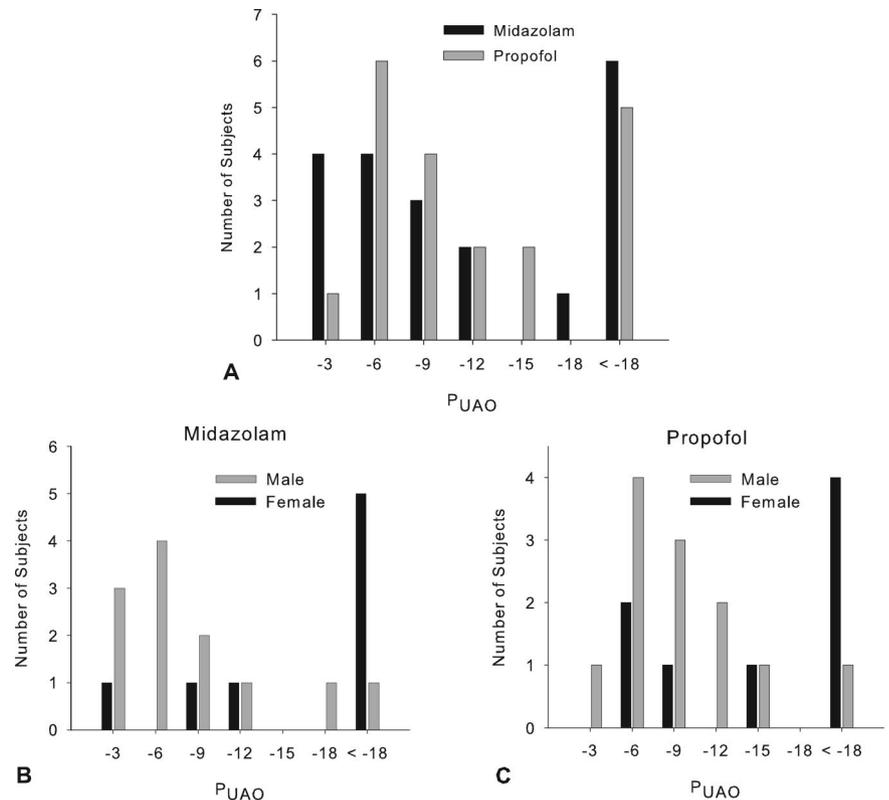


Fig. 2. Example of the response to decreasing airway pressure in one subject (signals as in fig. 1). Before the application of negative pressure in each of the panels, normal rounded inspiratory flows and synchrony of the abdomen and chest signals are seen. At -3 cm H_2O (A) and -6 cm H_2O (B), reduction and flattening of the inspiratory flow along with a phase shift in the respiratory inductance plethysmography (RIP) signals is seen, indicating partial airway obstruction. In C (-9 cm H_2O), after a single partially obstructed breath, complete obstruction occurs with no airflow and out-of-phase abdomen and chest respiratory inductance plethysmography signals. Note the immediate return to a normal unobstructed breathing pattern after relief of the negative pressure.

sure episodes did not clearly differentiate between early and late hypoxia, they were combined for analysis. There were 158 total negative challenges made during hypoxia: 17% were at a more negative pressure than that

subject's P_{UAO} (for each drug), 32% were equal to the P_{UAO} , and 51% were at a less negative pressure. Complete airway obstruction with these negative-pressure challenges only occurred eight times in four subjects, all

Fig. 3. Histograms of the pressure at which upper airway obstruction occurs (P_{UAO}) by subject, comparing the two drugs (A) and sex for midazolam (B) and propofol (C). See text for statistical significance.



male. Only one obstruction occurred with propofol, and seven occurred with midazolam. Although the numbers are too small for a valid statistical analysis, it is interesting that with these male subjects and midazolam, most (five of six) of the pressures required to produce obstruction were more negative than the P_{UAO} producing obstruction during sedation under hyperoxic conditions. Although we have no data relating to the statistics of the repeatability of the P_{UAO} determination in these subjects, we would expect that a DNAP equal to or more negative than the P_{UAO} should cause airway obstruction in most cases.

During the 5-min period before the first negative pressure, there were episodes of respiratory arousals (see Materials and Methods and fig. 1) that were not present in the control (unsedated) experiment. A few subjects had quite irregular breathing patterns, making it difficult to score the number of arousals. We were conservative in deciding when an arousal occurred. There was no difference in the incidence of arousals between male and female participants in any of the experiments. During the sedation in hyperoxia, there was no difference ($P = 0.2$) between the drugs (1.5 ± 2.2 vs. 0.7 ± 1.4 arousals for midazolam and propofol, respectively). During the recovery periods, there were no arousals for propofol, but at 15 and 45 min, there were 1.2 ± 2.1 and 1.0 ± 1.8 arousals, respectively, for midazolam ($P = 0.2$ for both). There was no difference in the incidence of arousals between male and female subjects.

Discussion

This study has yielded several important results as well as suggestions for future investigation. The most important and original finding is that for equivalent levels of sedation (as measured by both BIS and OAA/S scores), propofol and midazolam have similar but variable propensities for upper airway obstruction across subjects. This finding is particularly relevant in light of the existing controversies surrounding the administration of propofol instead of midazolam by nonanesthesiologists for moderate sedation. In addition, and not unexpectedly, the administration of both drugs was associated with respiratory arousals in some but not all subjects. As would be predicted by the pharmacokinetics of the drugs, the recovery from propofol sedation was more rapid and respiratory arousals disappeared more quickly (by 15 min) after the termination of the propofol infusion when compared with midazolam. We also found that similarly to reports of patients with sleep apnea, males were more susceptible to airway obstruction than females for both midazolam and propofol.

Our method of determining P_{UAO} differs from the determination of the critical airway pressure (P_{crit}) in that the resolution is 3 cm H₂O because we are not interpolating between pressures.⁷ In general, adjusting the pressure in the upper airway above and below ambient pressure has been frequently used to assess sleep apnea patients⁷ and drug-induced airway collapsibility. These studies often attempt to extrapolate to the pressure

causing zero flow (P_{crit}) using the peak inspiratory flows plotted *versus* the applied pressure. Although our method has a more definite end point (*i.e.*, actual UAO is observed), we could be estimating a more negative P_{UAO} than the P_{crit} obtained by extrapolating by as much as 3 cm H_2O . However, because it is unlikely that such a small difference could have clinical significance, we decided to use a method not using interpolation and allowing the measurement of a more definite end point.

A previous study in our laboratory³ using midazolam to achieve similar OAA/S and BIS endpoints found an average P_{crit} of -8.2 ± 4.3 cm H_2O . Although all subjects were reported to have a P_{crit} more positive than -20 cm H_2O , that study included only four women. Eastwood *et al.*¹⁷ recently reported on the effects of three levels of propofol anesthesia on P_{crit} . They also used target-controlled infusions but to 2.5–6.0 $\mu\text{g/ml}$ rather than the 1 $\mu\text{g/ml}$ concentration used by us. They found a correspondingly lower BIS and more positive P_{crit} (-0.3 ± 3.5 to 1.4 ± 3.5 cm H_2O). There was only one woman among their 12 subjects, but interestingly, she was one of only 3 subjects whose P_{crit} remained negative even at the deepest level of propofol anesthesia. Our sedative level of propofol provides another point on the concentration–response curve and emphasizes the large subject-to-subject variability when sedative levels of the drugs are used (fig. 3).

Eastwood *et al.*⁴ also found a dose–response effect of isoflurane with a P_{crit} of 1.1 ± 3.5 cm H_2O for 1.2% isoflurane and a P_{crit} of -0.2 ± 3.6 cm H_2O for 0.4% isoflurane in 14 male and 2 female subjects. As with propofol, the clinical significance of this small difference is unknown. Eastwood *et al.*¹⁸ also found a correlation between the isoflurane value of P_{crit} and the subsequent measurement of the apnea hypopnea index in a sleep study.

The much less negative values found by Eastwood *et al.* compared with those in this study may be due to the deeper level of sedation or anesthesia achieved, the differences in the drugs studied, or use of a patient rather than a healthy subject population, in addition to other unknown factors.

Several studies also have examined the effects of midazolam on the functioning of the upper airway and the occurrence of respiratory arrhythmias. Bailey *et al.*¹⁹ did not observe any respiratory arrhythmias with midazolam alone, but arrhythmias did occur when midazolam was combined with fentanyl. Masuda *et al.*²⁰ found that a bolus of midazolam (0.1 mg/kg) caused transient irregular breathing periods with an increase in rib cage motion and a decrease in abdominal motion with inspiratory snoring. These effects were seen more often in female than in male subjects. Morel *et al.*²¹ found an increase in the rib cage component of tidal volume and also commented on observing central apneas in six of eight subjects, most commonly between 2 and 4 min after the

bolus injection of 0.1 mg/kg midazolam. Although both Oshima *et al.*²² and Montravers *et al.*²³ found that midazolam increased upper airway resistance, Oshima *et al.* found only obstructive apneas, whereas Montravers *et al.* found central apneas. Oshima *et al.* related this to the slower administration of midazolam in their study without the higher peak plasma levels of midazolam causing the central apneas seen with the rapid bolus doses used by Montravers *et al.* However, we observed central apneas despite the use of an effect site target computer controller that prevented the high peak midazolam levels caused by a single bolus.

Except for a more rapid recovery, we found little difference in respiratory arousals between propofol and midazolam. We speculate that the lack of correlation between arousals or respiratory arrhythmias and P_{UAO} is due to the different factors primarily responsible for controlling these phenomena. The respiratory arrhythmias are caused primarily by the drug effect on medullary-pontine respiratory rhythm and pattern generation, although airway collapsibility may result in mixed central and obstructive apneas (*e.g.*, fig. 1). However, P_{UAO} is primarily a measure of airway collapsibility. This, plus the loss of wakefulness and the attendant loss of neuromuscular tone and airway drive function caused by either drug, results in the observation of greater collapsibility of the airway in males *versus* females, similar to airway function as seen during sleep. Further research will be necessary to advance this hypothesis and to better define the relation between P_{UAO} and spontaneous respiratory arrhythmias.

The male and female subjects in our study population had comparable BMIs and Epworth Sleepiness Scale scores and are unlikely to have clinical obstructive sleep apnea. Nevertheless, there are interesting comparisons regarding breathing during sleep and sedation. Premenopausal women have a much lower incidence of both sleep apnea and sleep-disordered breathing when compared with men.⁸ The reasons for this difference are multifactorial and incompletely understood but include differences in fat distribution, sex hormones, upper airway functional (dynamic and static) properties, neural control, and obesity-related humeral factors.^{24–28} It remains unclear to what degree differences in upper airway function between men and women are physiologic or anatomical in basis. Any physiologic differences could be particularly relevant to our study because they might explain our observed differences in the susceptibility to airway obstruction during sedation.

Trinder *et al.*²⁹ found that in young subjects with normal BMI, sleep onset caused a similar decrease in ventilation and increase in upper airway resistance in men and women, but as nonrapid eye movement sleep became established, upper airway resistance continued to increase in men but not in women. They speculated that this difference was due to a sex difference in the

effect of sleep on upper airway muscle activity. However, Pillar *et al.*³⁰ measured the genioglossal and tensor palatine electromyograms during added inspiratory resistive loads in healthy men and women during sleep and concluded that the greater collapsibility in men was not due to any difference in airway dilator muscle activation. The results of Trinder *et al.* were also not replicated by Thurnheer *et al.*,³¹ who were unable to find any sex differences in the increase in airway resistance with sleep in young healthy subjects. They hypothesized that methodologic differences between the two studies accounted for the inconsistent findings.

Particularly relevant to our study are the data of Rowley *et al.*,⁹ who used negative airway pressure to measure P_{crit} in men and women during sleep. They found no sex difference in measured P_{crit} or in the increase of airway resistance with sleep, speculating that the rapid application of negative pressure, as in our study, would result in a reflex activation of the genioglossus muscle and that P_{crit} is primarily determined by the neuromuscular response of this reflex. Further, they postulated that the difference between men and women was due to mechanical properties of the upper airway. We may have found a sex difference in P_{UAO} because of the sedative depression of this negative-pressure reflex, thus making the sex differences in airway mechanics more apparent. The hypoglossal motor neurons may be inhibited by γ -aminobutyric acid and/or glycine (see Horner³² for a recent review) and could be sensitive to the effects of midazolam and propofol.

Rowley *et al.*³³ also examined upper airway compliance using fiberoptic endoscopy and found that retro-palatal compliance was higher in men than in women, both in the awake state and during nonrapid eye movement sleep. However, this sex difference could be solely explained by a difference in neck circumference (*i.e.*, an anatomical difference), and they proposed that the differences in soft tissue volume of the neck between men and women, and not a specific sex difference, caused the difference in compliance. Using magnetic resonance imaging, Malhotra *et al.*²⁵ emphasized that the difference in the length of the airway between men and women, as well as an increase in soft palate size, also contributed to the increased collapsibility of the upper airway in men. However, in patients with sleep apnea, although the neck-to-height ratio was the most significant predictor of apnea hypopnea index, factors other than age, such as BMI and neck circumference, also may be important.³⁴

The fact that some subjects did not obstruct, even at -18 cm H_2O in our apparently homogeneous group of healthy subjects, suggests that a significant variability in the tendency for airway collapse exists. However, there are possibly more subtle anatomical, physiologic, or neurohumoral factors underlying the relative stiffness of the airway in this subset of subjects. Identifying these factors could provide information about possible predictive and

preventive factors for airway obstruction during sedation. Another area for future research is the role of increased respiratory drive (*e.g.*, from hypoxia) in preventing airway collapse.

In summary, we have compared the propensity for airway obstruction during sedation with midazolam or propofol, using a negative airway pressure challenge. We found no difference between the two drugs and their effects on ventilation and airway collapsibility caused by DNAP during the sedation. We did observe a greater propensity for airway collapse in males, whether sedated with either propofol or midazolam. As would be expected from the drugs' pharmacokinetic profiles, recovery of airway function after sedation was faster with propofol. Our findings do not suggest that the use of propofol for moderate sedation, when compared with the use of midazolam, is inherently more likely to result in airway obstruction in healthy subjects. However, patient and pharmacokinetic factors beyond those explored in this study must be considered if these drugs are to be used in a safe manner during moderate levels of sedation.

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