

ANESTHESIOLOGY

Upper Airway Collapsibility during Dexmedetomidine and Propofol Sedation in Healthy Volunteers

A Nonblinded Randomized Crossover Study

Åse Lodenius, M.D., Ph.D., D.E.S.A.,
Kathleen J. Maddison, Ph.D., Brad K. Lawther, M.D.,
Mika Scheinin, M.D., Ph.D.,
Lars I. Eriksson, M.D., Ph.D., F.R.C.A.,
Peter R. Eastwood, Ph.D., David R. Hillman, M.B.B.S.,
Malin Jonsson Fagerlund, M.D., Ph.D., D.E.S.A.,
Jennifer H. Walsh, M.Sc., Ph.D.

ANESTHESIOLOGY 2019; 131:962–73

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dexmedetomidine is a relatively new sedative promoted as having minimal effect on ventilatory drive or the propensity to upper airway obstruction

What This Article Tells Us That Is New

- At comparable levels of light to moderate sedation, dexmedetomidine and propofol exhibit similar degrees of pharyngeal collapsibility and reductions in ventilatory drive
- The findings suggest that sedation with dexmedetomidine does not offer inherent protection against upper airway obstruction or ventilatory depression

ABSTRACT

Background: Dexmedetomidine is a sedative promoted as having minimal impact on ventilatory drive or upper airway muscle activity. However, a trial recently demonstrated impaired ventilatory drive and induction of apneas in sedated volunteers. The present study measured upper airway collapsibility during dexmedetomidine sedation and related it to propofol.

Methods: Twelve volunteers (seven female) entered this nonblinded, randomized crossover study. Upper airway collapsibility (pharyngeal critical pressure) was measured during low and moderate infusion rates of propofol or dexmedetomidine. A bolus dose was followed by low ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or $42 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and moderate ($1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or $83 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) rates of infusion of dexmedetomidine and propofol, respectively.

Results: Complete data sets were obtained from nine volunteers (median age [range], 46 [23 to 66] yr; body mass index, 25.4 [20.3 to 32.4] kg/m^2). The Bispectral Index score at time of pharyngeal critical pressure measurements was 74 ± 10 and 65 ± 13 (mean difference, 9; 95% CI, 3 to 16; $P = 0.011$) during low infusion rates versus 57 ± 16 and 39 ± 12 (mean difference, 18; 95% CI, 8 to 28; $P = 0.003$) during moderate infusion rates of dexmedetomidine and propofol, respectively. A difference in pharyngeal critical pressure during sedation with dexmedetomidine or propofol could not be shown at either the low or moderate infusion rate. Median (interquartile range) pharyngeal critical pressure was -2.0 (less than -15 to 2.3) and 0.9 (less than -15 to 1.5) $\text{cm H}_2\text{O}$ (mean difference, 0.9; 95% CI, -4.7 to 3.1) during low infusion rates ($P = 0.595$) versus -0.3 (-9.2 to 1.4) and -0.6 (-7.7 to 1.3) $\text{cm H}_2\text{O}$ (mean difference, 0.0; 95% CI, -2.1 to 2.1; $P = 0.980$) during moderate infusion of dexmedetomidine and propofol, respectively. A strong linear relationship between pharyngeal critical pressure during dexmedetomidine and propofol sedation was evident at low ($r = 0.82$; $P = 0.007$) and moderate ($r = 0.90$; $P < 0.001$) infusion rates.

Conclusions: These observations suggest that dexmedetomidine sedation does not inherently protect against upper airway obstruction.

(ANESTHESIOLOGY 2019; 131:962–73)

Upper airway obstruction and respiratory depression are common side effects of many sedative and anesthetic agents and may put ventilation and oxygenation at risk.^{1–4} A drug that can offer sedation without impairing airway patency and increasing risk of hypoxemia would be ideal in situations where preservation of spontaneous ventilation is desired, such as during sedation in nonintubated patients in intensive care or during diagnostic procedures

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 953. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the Upper Airway Symposium in Clare Valley, South Australia, Australia, February 7–9, 2018 and at the Australasian Sleep Association Annual Scientific Meeting in Brisbane Australia, October 17–20, 2018.

Submitted for publication October 8, 2018. Accepted for publication June 11, 2019. Corrected on December 11, 2019. From the Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, and the Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care, Karolinska Institutet, Stockholm, Sweden (A.L., L.I.E., M.J.F.); the West Australian Sleep Disorders Research Institute, Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia (K.J.M., P.R.E., D.R.H., J.H.W.); the Centre for Sleep Science, School of Human Sciences (K.J.M., P.R.E., D.R.H., J.H.W.) and the Department of Anaesthesia, Sir Charles Gairdner Hospital (B.K.L.), Nedlands, Western Australia, Australia; and the Institute of Biomedicine, University of Turku, and Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland (M.S.).

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or awake tracheal intubation. Dexmedetomidine, a highly selective α_2 -adrenoceptor agonist,^{5,6} has been advocated for use in these patient populations because the drug has been considered to lack respiratory side effects.⁷⁻⁹

However, this notion has been challenged by findings from several recent studies. Drug-induced sedation endoscopy studies have shown obstruction of the upper airway at moderate levels of sedation with dexmedetomidine.¹⁰ A reduction in airway dimensions has also been observed during magnetic resonance imaging of the upper airway in children sedated with dexmedetomidine.¹¹ Further, we recently demonstrated that light to moderate sedation with dexmedetomidine or propofol in adult volunteers caused similar reductions in ventilatory responses to hypoxia and hypercapnia with either drug.¹² Moreover, that study also displayed serious upper airway compromise with almost all participants exhibiting repetitive episodes of snoring and upper airway obstruction during dexmedetomidine sedation, whereas less than half had such events during propofol sedation.¹²

Hence, there is reason to doubt the assertion that use of dexmedetomidine provides sedation without airway compromise. However, no previous study has directly measured upper airway collapsibility during dexmedetomidine sedation in adults or used such measures to compare it with conditions during propofol sedation, a suitable benchmark sedative agent given its well characterized effects on upper airway collapsibility.^{2,13} This study addresses this deficiency, using pharyngeal critical pressure, a widely used measure of collapsibility that assesses the intraluminal pressure at which airway closure occurs. Such quantification allows precise assessment of the effects of sedation on airway patency, facilitating comparisons between drug levels and different agents.

The aim of the present study was to establish whether upper airway collapsibility is increased during dexmedetomidine sedation in healthy adult volunteers. We examined the hypothesis that dexmedetomidine sedation would have less effect on upper airway collapsibility than propofol sedation. Participants were to be given dexmedetomidine to achieve light and moderate levels of sedation. This was to be compared to sedation with propofol, a sedative known to increase upper airway collapsibility. The primary endpoint of the study was the effect of dexmedetomidine on upper airway collapsibility, quantified by pharyngeal critical pressure, relative to standard intravenous sedation with propofol. The purpose of undertaking the study was to test the assertion that dexmedetomidine sedation offers protection against obstruction of the unprotected upper airway.

If indeed, dexmedetomidine proved to offer such protection, then it would offer advantages for sedation in nonintubated patients. If not, uninformed use of dexmedetomidine in these situations could compromise patient safety.

Materials and Methods

Ethics

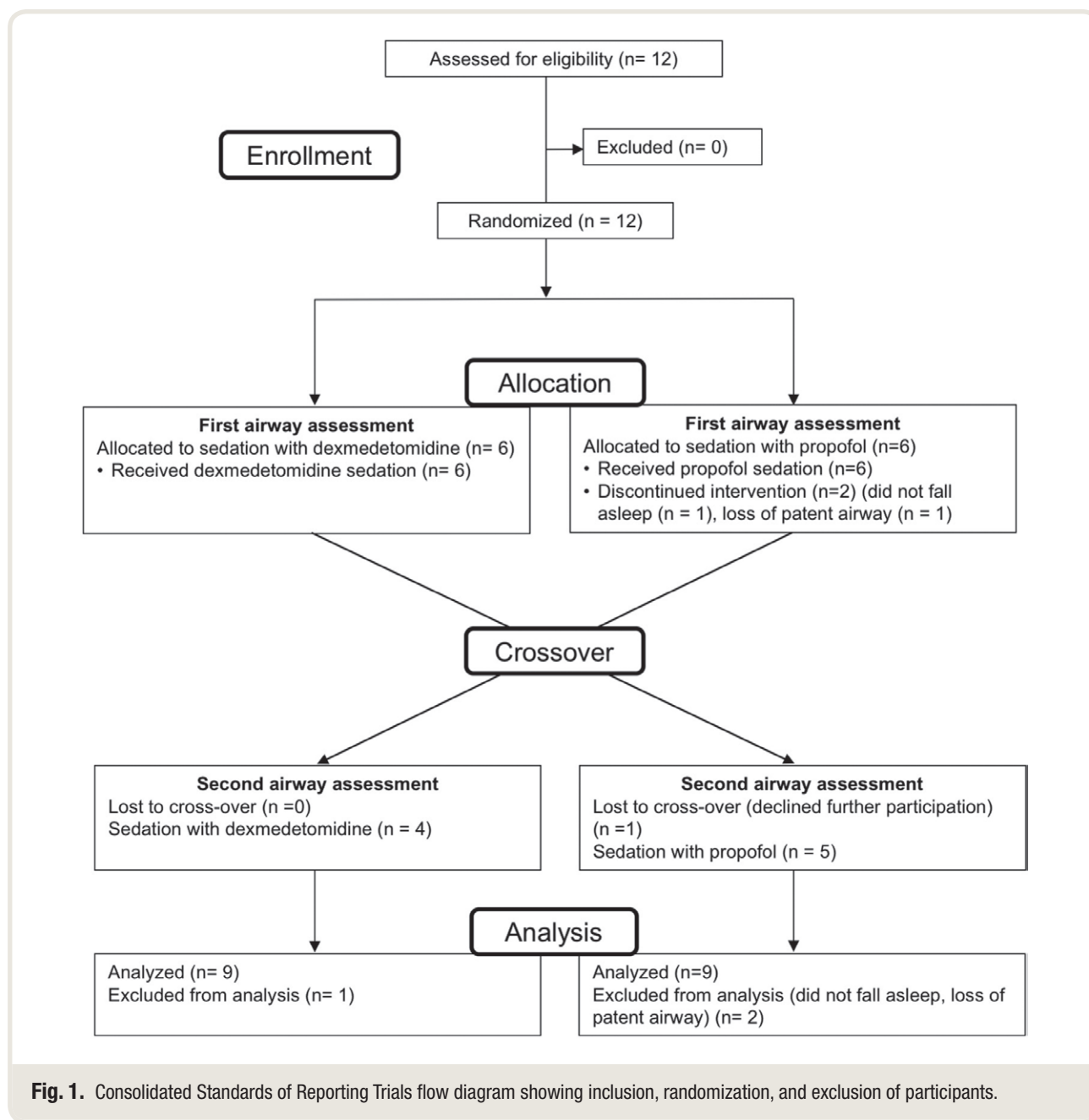
This study was approved by the Sir Charles Gairdner Hospital Human Research Ethics Committee (Perth, Western Australia; approval No. 2009-037). The trial was conducted according to the standard of the Declaration of Helsinki, Good Clinical Practice, and the Consolidated Standards of Reporting Trials guidelines (Supplemental Digital Content, <http://links.lww.com/ALN/C52>). The study was registered with the Australian New Zealand Clinical Trials Registry (trial ACTRN12616000085471). The Universal Trial Number is U1111-1175-8788. Through oversight, registration was completed after study commencement, but no modification of the original protocol was made from commencement. A more detailed protocol can be provided by request.

The study was performed from August 2015 to September 2016 at the research facilities at the West Australian Sleep Disorders Research Institute, Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia. Analyses of plasma propofol concentrations were made at the Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care, Karolinska Institutet, Stockholm, Sweden. Plasma dexmedetomidine concentrations were analyzed at the Clinical Research Services Turku, University of Turku, Finland.

Study Subjects. Eligible participants in this randomized, cross-over study were nonsmoking adults (age 18 to 65 yr), with an American Society of Anesthesiologists (ASA) physical status score of I or II and a body mass index of less than 37 kg/m². Predisposition to obstructive sleep apnea was assessed with the STOP-BANG questionnaire. Exclusion criteria were allergy to the study drugs, upper airway pathology, severe obstructive sleep apnea, uncontrolled cardiovascular or respiratory disease, or other systemic disorder. Participants were recruited through advertising at an affiliated university campus or sleep research institute or from individuals previously known by the study team. They were randomized and assigned for intervention by the study team after oral and written informed consent.

Randomization was undertaken to establish the order of sedation with dexmedetomidine or propofol in a first block of five volunteers, followed by a second block of seven volunteers, using an online resource.¹⁴ Concealment regarding randomization was not made. A crossover design was used, each volunteer acting as his/her own control with a minimum interval of 48 h between administration of each drug protocol (fig. 1). Blinding of the intervention was considered difficult because of the different colors of the study drug infusions and their palpably different pharmacokinetics and was therefore not done. The entire study team was involved in data collection, and therefore the study drug was not concealed during data analysis.

Participant Preparation and Monitoring. No premedication was administered. Standard perioperative monitoring was applied. An intravenous cannula was placed in each arm, one used for drug and compound sodium lactate administration (Viaflex;



Baxter, Australia) and the other used for venous blood sampling. Transcutaneous carbon dioxide (TCM 4 series; Radiometer Medical ApS, Denmark) and Bispectral Index score (A-2000 Bispectral Index score monitor) were continuously recorded along with a three-lead electroencephalogram (O1, C3, F3).

The participants were supine with the head maintained in the neutral position (Frankfort plane perpendicular to the bed surface) using a modified Shea headrest. A volume-calibrated pneumotachograph (Korr Medical Technologies, USA), an expiratory port, and a custom-built pressure source (ResMed, Australia) capable of delivering positive and negative pressure (+20 to -20 cm H₂O) were connected in series to a well sealed nasal mask. Nasal mask pressure was continuously

measured from a sample port in the mask connected to a pressure transducer (model 143 PC, Micro Switch; Honeywell, USA). Maintenance nasal pressure was the pressure at which inspiratory flow limitation was abolished and was applied at all times other than when measures of airway collapsibility were being performed.^{15,16} An air-oxygen mix (FiO₂ ~0.5) was delivered *via* a Bain circuit attached to the pressure source and the nasal mask, at a minimum flow of 10 l/min. The mouth was sealed with occlusive tape, and a chin strap was fitted.

A calibrated four-sensor pressure transducer catheter (CTO-4; Gael Tec, United Kingdom) was passed into the esophagus, as previously described,¹⁷ to measure respiratory effort by pharyngeal and esophageal pressures during

flow-limited breathing, as well as retropalatal and hypopharyngeal pressures. In addition, thoracic and abdominal respiratory inductance plethysmography (Respirace; Ambulatory Monitoring, USA) was applied. All signals were recorded continuously at 1,000 Hz on a Power Lab data acquisition and analysis system (model 16s; AD Instruments, Australia).

Sedation during Study Protocol. Sedation was initiated using clinically accepted set dosages targeting light and deep sedation. A standard syringe pump (Alaris PK; Cardinal Health, Switzerland) was used to deliver a bolus infusion over 10 min of either dexmedetomidine (Precedex; Hospira Inc., USA) $0.6 \mu\text{g}/\text{kg}$ or propofol (Diprivan; Astra Zeneca, Australia) $750 \mu\text{g}/\text{kg}$. This was followed by continuous infusion of dexmedetomidine $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or propofol $42 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, aiming for light sedation. The first set of measurements of airway collapsibility was done at least 20 min after the start of the maintenance dose to allow for a steady state to occur.

Immediately after these measurements, the infusion rate was increased to dexmedetomidine $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ or propofol $83 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, aiming for deep sedation. The second set of airway collapsibility measurements was performed 20 min after initiation of this higher infusion rate (fig. 2).

Sedation level was monitored with continuous electroencephalogram, Bispectral Index score recordings, and two clinical sedation scales scored at discrete points of time (fig. 2). The modified five-point composite Observer's Assessment of Alertness/Sedation scale¹⁸ and the Richmond Agitation-Sedation Scale¹⁹ were used on two occasions for each infusion rate: 10 min after the start of each maintenance dose and immediately after airway measurements were completed. These times were selected for sedation checks to avoid provoking arousal and possible interference with airway measurements. Blood samples were collected for analysis of plasma

concentrations of dexmedetomidine or propofol before sedation (baseline value) and after completion of airway measurements at each infusion rate. After the second airway measurement, the infusion was stopped, and the protocol was ended.

Upper Airway Collapsibility Measurement: Pharyngeal Critical Pressure. Upper airway collapsibility was assessed using pharyngeal critical pressure as previously described at each infusion rate (fig. 3).^{1,2,13,15–17,20} Briefly, stable breathing was established at a maintenance nasal pressure level ("maintenance pressure") sufficient to abolish inspiratory flow limitation (the presence of which was recognized by appearance of a plateau in the inspiratory flow profile or a failure of inspiratory flow to increase despite a decrease in esophageal pressure of at least $1 \text{ cm H}_2\text{O}$). The mask pressure was abruptly reduced from maintenance pressure to a range of positive and, if necessary, negative pressures to induce variable degrees of inspiratory flow limitation over a five-breath sequence before a return to maintenance pressure. End-expiratory pressure and mid-inspiratory flow for each of breaths 3–5 of the pressure drop were measured, and a mean was calculated. A minimum of three pressure drops to levels associated with flow limitation was obtained. Pharyngeal critical pressure was derived from linear regression of the mask pressure–plateau flow rate relationship during these pressure drops to calculate the pressure at which zero flow occurs (fig. 3). If brief arousal (less than 45 s of increase in electroencephalogram frequency followed by return to the previous state) occurred during a pressure drop or a pressure-drop sequence, any affected pressure levels were excluded from the pharyngeal critical pressure analysis and repeated. However, if the participant aroused for a more lengthy period, the entire pressure-drop sequence was abandoned, and a new

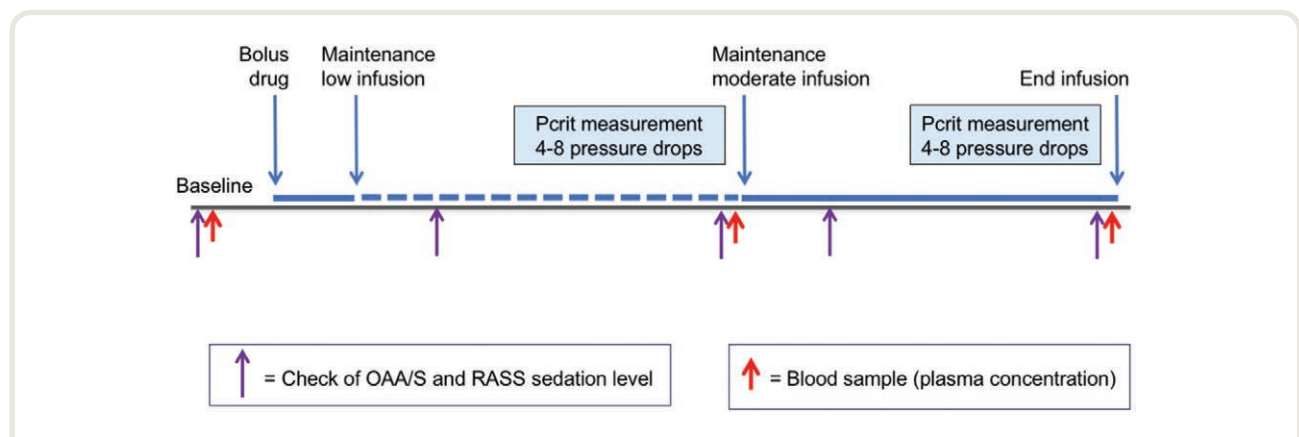


Fig. 2. Protocol used for sedation and acquisition of upper airway collapsibility data during dexmedetomidine or propofol sedation. Sedation was assessed with the modified five-point composite Observer's Assessment of Alertness/Sedation (OAA/S) scale and the Richmond Agitation-Sedation Scale (RASS). The sedation scale scores were as follows: (1) OAA/S scores 1: deep sedation, 2 to 4: light to moderate sedation, and 5: alert state; and (2) RASS score 0: alert and calm, -1: sustained awakening more than 10 s to voice, -2: briefly awakens to voice less than 10 s, -3: movement to voice but no eye contact, -4: movement to physical stimulation, and -5: unarousable. Pcrit, pharyngeal critical pressure.

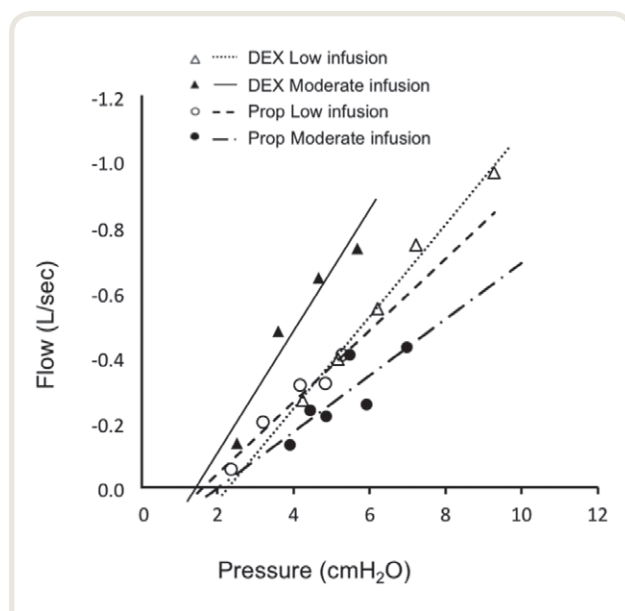


Fig. 3. A representative graph showing linear regression of airway flow and airway pressure in flow limited breaths used for pharyngeal critical pressure calculation during sedation with low and moderate infusion rates of dexmedetomidine and propofol in one individual (No. 7). Open triangles with dotted line indicate dexmedetomidine low infusion. Closed triangles with solid line indicate dexmedetomidine moderate infusion. Open circles with dashed line indicate propofol low infusion. Closed circles with dash-dot line indicate propofol moderate infusion. DEX, dexmedetomidine; Prop, propofol.

sequence was initiated after return to a stable level of sedation and breathing. The pressure drops were limited to a minimum of -10 cm H₂O (a level indicative of an airway highly resistant to collapse) as a precaution against untoward reflex responses, arousal, or gastroesophageal reflux. If a pharyngeal critical pressure was unable to be generated with this minimum pressure and flow limitation was not present to allow extrapolation of the flow–pressure relationship to zero flow (so a pharyngeal critical pressure value could be derived at a pressure greater than -15 cm H₂O),¹ then a pharyngeal critical pressure value of less than -15 cm H₂O was recorded.

Analysis of Plasma Concentrations of Dexmedetomidine and Propofol. Blood was collected for measurement of drug concentrations in plasma before sedation and after completion of airway measurements at each infusion rate. Five ml of venous blood was drawn from the arm contralateral to drug infusion and placed into EDTA-containing tubes that were stored in wet ice and centrifuged at $+4^{\circ}\text{C}$ for 10 min at 1,500g within 3 h. The plasma was then immediately transferred to precooled polypropylene tubes and frozen at -20°C or colder. Concentrations of dexmedetomidine and propofol in plasma were determined as described previously.¹²

Statistical Analysis. Because data relating to upper airway collapsibility and dexmedetomidine sedation was unavailable, a prospective sample size estimate was generated partly based on earlier studies by the research group in Perth with a difference in pharyngeal critical pressure of 3 cm H₂O, considered to be of clinical significance, and a variability of 3.4.²¹ An interim analysis was performed after completion of $n = 12$ participants, with complete data available from $n = 9$. No adjustments were made to the P values for this interim analysis. Power analysis at that time indicated insufficient power to detect a difference in pharyngeal critical pressure between dexmedetomidine and propofol sedation or confirm equivalence, based on the sample size and data available. A significantly larger sample would be required to do this. Given the need for a sample size widely exceeding the one originally calculated, the demanding nature of the study, and the consequent difficulty with subject recruitment, the study was ended.

Continuous data are presented as means \pm SD or median (interquartile range). Categorical data are expressed as medians (interquartile range) or numbers. Normal distributions of data were tested using histograms, Q–Q plots, and the Shapiro–Wilk’s test.

The primary outcome variable, pharyngeal critical pressure, was compared between drugs, dexmedetomidine and propofol, on two different occasions: “low infusion rate” and “moderate infusion rate,” using a generalized equation estimation model to account for the repeated measures and a small sample size. If there was no sign of airway collapse, we used the Winsorizing method to reduce bias by the effect of extreme outliers, replacing the pharyngeal critical pressure value with a value of -15 cm H₂O. These values were also used in Pearson correlation analyses, performed to identify the strength of the relationship between pharyngeal critical pressure during sedation with dexmedetomidine and pharyngeal critical pressure during propofol, at both infusion rates.

Bispectral Index score, mean arterial blood pressure, heart rate, and transcutaneous carbon dioxide were compared between drugs at seven different occasions using two-tailed testing with repeated-measures ANOVA with two within factors: time and drug. If differences were revealed by the repeated-measures ANOVA, preplanned pairwise comparison between drugs was made using a Bonferroni *post hoc* test. Sedation levels according to sedation scales Observer’s Assessment of Alertness/Sedation and Richmond Agitation–Sedation Scale were compared with a sign test. Bispectral Index score and transcutaneous carbon dioxide were averaged over predefined time periods and are presented as means \pm SD. A P value of less than 0.05 was considered statistically significant. All statistical analyses were undertaken using IBM SPSS Statistics version 24 software (IBM, USA). Graphs were made using Prism 7.0 (GraphPad, USA).

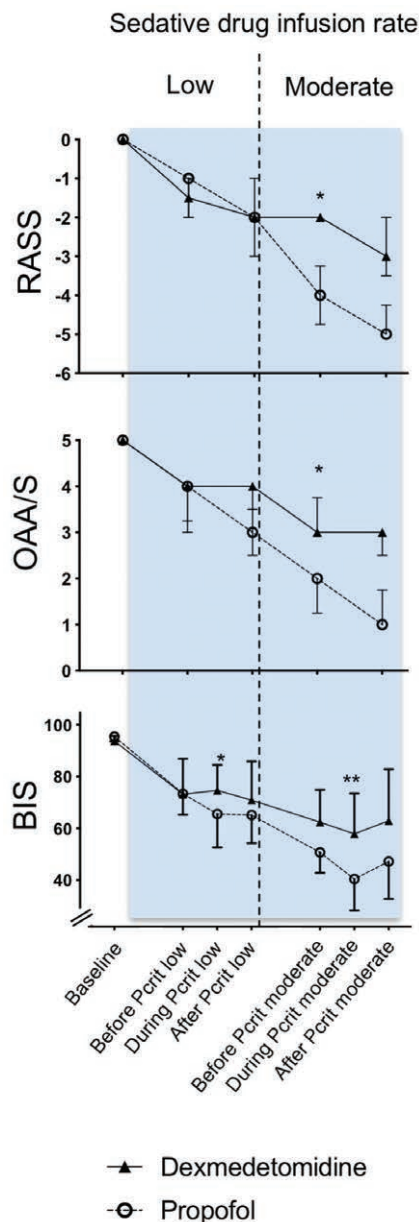


Fig. 4. Richmond Agitation Sedation Scale (RASS), modified 5-point composite Observer's Assessment of Alertness/Sedation (OAA/S), and Bispectral Index score (BIS) before and during sedation with dexmedetomidine (closed triangles with solid line) or propofol (open circles with dotted line). The shaded area shows the time for sedation with drug infusion at low and moderate rates. Sedation checks, OAA/S, and RASS, were conducted at baseline and before and immediately after airway measurements. BIS was recorded before, during, and after airway measurements. The vertical broken line indicates the time point when the infusion rate was changed from low to moderate. Data are presented as means \pm SD for BIS and as median (interquartile range) for OAA/S and RASS. Please note that error bars of SD are unidirectional for clarity. If no error bars are visible they are smaller than the symbols. * $P < 0.05$; ** $P < 0.01$.

Results

Twelve subjects, seven female, were included in this study. They had a median (range) age of 46 (23 to 66) years, body mass index of 25.4 (20.3 to 32.4) kg/m^2 , and ASA physical status score of 1.5 (I to II). The six subjects with ASA class II comprised two subjects with treated hypothyroidism, two with hyperlipidemia and/or non-insulin-dependent diabetes mellitus, and one with treated hypertension. Their modified Mallampati score was 1 (1 to 4), thyromental distance was 10 (8 to 12) cm, and neck circumference was 35 (31 to 45) cm. Data regarding thyromental distance were missing for two participants. The STOP-BANG score was assessed and found to be 1 (0 to 5). The apnea hypopnea index had been determined in two subjects (No. 4 and No. 6) and was 25 and 7, respectively. Nine of twelve participants completed the full study protocol (fig. 1). Of the three other participants, one chose not to participate on the second occasion (propofol) because of time commitments, in one a patent airway could not be satisfactorily maintained without manual intervention, and one subject remained awake at the prescribed infusion rates. These three individuals lacked complete data for pharyngeal critical pressure measurements and were therefore excluded from analysis. Consequently, nine data sets evaluating upper airway behavior during both dexmedetomidine and propofol sedation were analyzed. No adverse events were experienced during the conduct of the study.

Sedation

The total time of drug infusion was 101 ± 11 min for dexmedetomidine and 100 ± 17 min for propofol. Assessment of airway collapsibility took 15 ± 6 versus 12 ± 7 min during low and 13 ± 8 versus 12 ± 10 min during moderate infusion rates for dexmedetomidine and propofol, respectively. Results from measurements of the Bispectral Index score, the modified Observer's Assessment of Alertness/Sedation, and the Richmond Agitation-Sedation Scale sedation scales are presented in figure 4.

Mean Bispectral Index score levels at the time of airway measurements were higher during dexmedetomidine infusion than propofol infusion during both low infusion rates 74 ± 10 and 65 ± 13 , with a mean difference of 9 (95% CI, 3 to 16), respectively ($P = 0.011$) and moderate infusion rates of 57 ± 16 and 39 ± 12 , mean difference of 18 (95% CI, 8 to 28), respectively ($P = 0.003$), but were similar between dexmedetomidine at moderate infusion rates and propofol at low infusion rates of 57 ± 16 versus 65 ± 13 , mean difference of 8 (95% CI, 0 to 16; $P = 0.048$; fig. 4). A statistical difference in sedation scale levels was not observed when dexmedetomidine and propofol were compared at low infusion rates but was observed during moderate infusion rates before pharyngeal critical pressure measurement for both Observer's Assessment of Alertness/Sedation (3.0 [3.0 to 4.0] vs. 2.0 [1.0 to 2.0], respectively; $P = 0.016$) and

Richmond Agitation–Sedation Scale (-2.0 [-2.0 to -2.0] vs. -4.0 [-3.25 to -4.75] respectively; $P = 0.016$; fig. 4).

Measurement of drug concentrations in plasma verified drug exposure. Specifically, the observed mean concentrations were 0.6 ± 0.1 and 1.6 ± 0.3 ng/ml at low and moderate infusion rates of dexmedetomidine and 0.9 ± 0.2 and 1.4 ± 0.2 μ g/ml during low and moderate infusion rates of propofol.

Primary Outcome: Upper Airway Collapsibility, Pharyngeal Critical Pressure, during Sedation with Dexmedetomidine or Propofol

The maintenance airway pressure required to prevent inspiratory flow limitation varied between 4 (the minimum maintenance pressure used) and 15 cm H₂O. The primary outcome, pharyngeal critical pressure, was -2.0 (less than -15 to 2.3) and 0.9 (less than -15 to 1.5) cm H₂O (mean difference, 0.9; 95% CI, -4.7 to 3.1) during low infusion rates versus -0.3 (-9.2 to 1.4) and -0.6 (-7.7 to 1.3) cm H₂O (mean difference, 0.0; 95% CI, -2.1 to 2.1) during moderate infusion of dexmedetomidine and propofol, respectively. In five participants, pharyngeal critical pressure was more than 0 cm H₂O (indicating upper airway obstruction at atmospheric pressure), and in two other participants, pharyngeal critical pressure was less than -15 cm H₂O (beyond the limit of our testing [Materials and Methods] and indicating high resistance to upper airway collapse) during sedation both with dexmedetomidine and with propofol at low and/or moderate infusion rates. In the remaining two participants, pharyngeal critical pressure was consistently less than 0 cm H₂O with both sedatives, although it was less than -15 cm H₂O with only one or the other sedative. Consistent with these concordant observations, a statistically

significant difference in pharyngeal critical pressure could not be shown during sedation with dexmedetomidine or propofol at either low the infusion rate ($P = 0.595$) or the moderate infusion rate ($P = 0.980$). Furthermore, a strong relationship between pharyngeal critical pressure during dexmedetomidine and propofol sedation was evident at the low and moderate infusion rates (fig. 5).

Effect of Sedation with Dexmedetomidine or Propofol on Respiration and Circulation

Three of the participants had periods of central apnea starting during the 10-min bolus dose administration of dexmedetomidine with durations up to 70 s: a representative polygraph example is shown in figure 6. These resolved at the latest within 3 min after completion of the bolus dose infusion. Apneic episodes were also seen in these same three individuals during propofol bolus dose administration, although the episodes were less frequent and of shorter duration than during dexmedetomidine infusion. In participant No. 3, seven apnea periods up to 60 s long during the dexmedetomidine bolus dose versus four apnea episodes with the longest duration of 50 s during the propofol bolus were recorded. Participant No. 5 had four apnea episodes, up to 30 s long, during bolus doses of both drugs. In participant No. 6, four apneas up to 75 s long were recorded in the last 4 min of the dexmedetomidine bolus dose infusion, and irregular breathing persisted for a further 5 min after completion of the bolus dose. This participant also exhibited three apnea episodes up to 50 s long during the propofol bolus infusion, beginning within 2 min from start of the bolus dose infusion. Apnea episodes resolved spontaneously with continued infusion in each case.

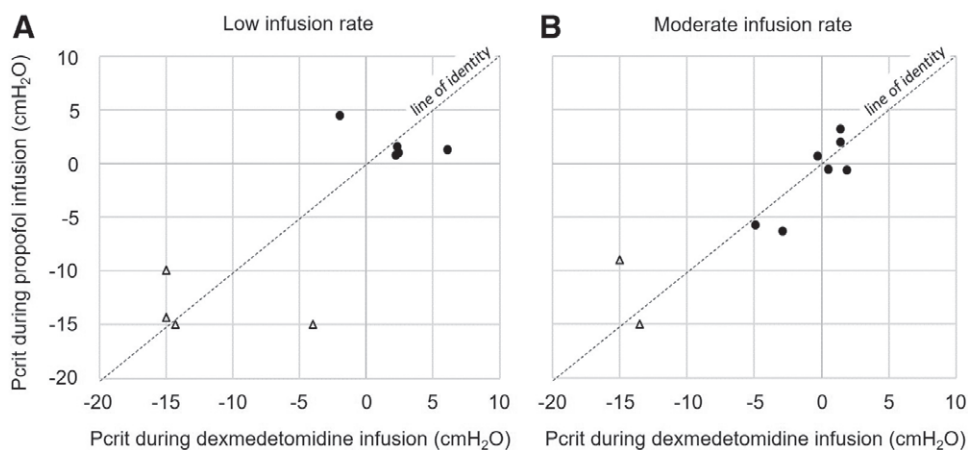


Fig. 5. Relationship between pharyngeal critical pressure (Pcrit) during dexmedetomidine and Pcrit propofol sedation during low (A) and moderate (B) infusion rates. *Open triangles* represent participants with an airway highly resistant to collapse (Pcrit was less than or equal to -15 cm H₂O). The *dotted line* indicates line of identity. Note the concordance between Pcrit values during sedation at low ($r = 0.82$; $P = 0.007$) and moderate ($r = 0.90$; $P < 0.001$) infusion rates with both drugs ($n = 9$).

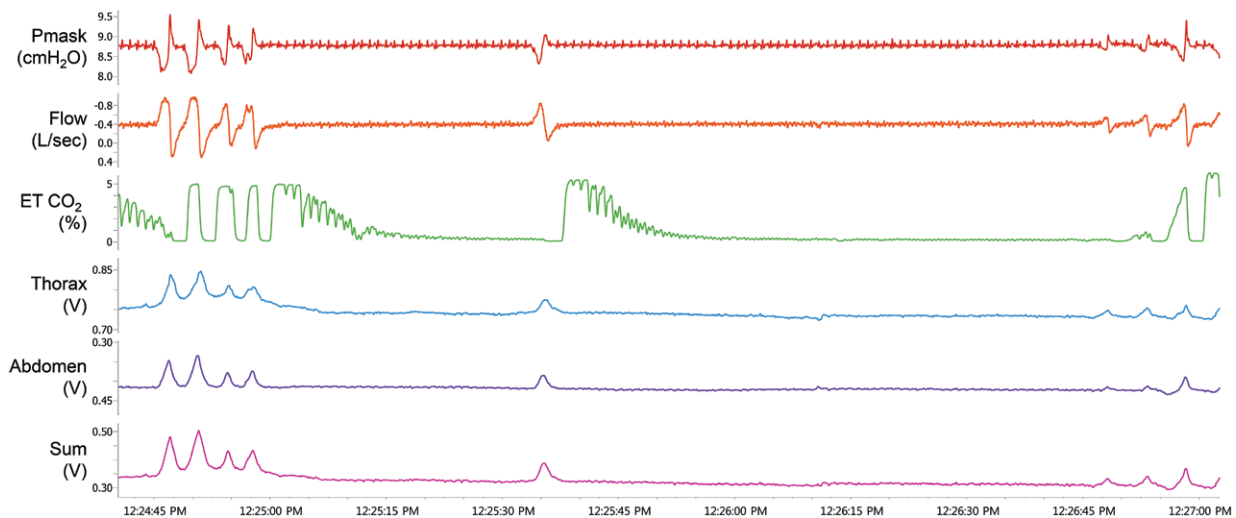


Fig. 6. Original data recording of apnea episodes in one subject (No. 3) appearing 7 min after induction of dexmedetomidine sedation with a bolus dose of 0.6 $\mu\text{g}/\text{kg}$ administered during 10 min. Rows 1 to 3 from the top display mask pressure (Pmask), airway flow (Flow) and end-tidal carbon dioxide (ET CO_2). In rows 4 to 6, inductance plethysmography of the thorax and abdomen show an absence of respiratory effort indicative of centrally evoked apnea.

Transcutaneous carbon dioxide at the end of bolus dose infusion did not differ between individuals with ($n = 3$) and without apnea during either dexmedetomidine (42 ± 4 vs. 48 ± 2 mmHg; $P = 0.570$) or propofol (46 ± 7 vs. 47 ± 4 mmHg; $P = 0.857$) infusion. Transcutaneous carbon dioxide increased to a similar extent from baseline to the end

of the sedation protocol with dexmedetomidine (from 41 ± 5 to 47 ± 4 mmHg) and propofol sedation (from 42 ± 5 to 48 ± 6 mmHg) with no statistically significant difference between drugs ($P = 0.281$; fig. 7).

Peripheral oxygen saturation did not decrease below 96% at any time in any participant. Mean heart rate was lower during dexmedetomidine compared with propofol sedation ($P = 0.001$), but mean arterial blood pressure was similar during infusion of both agents ($P = 0.297$; fig. 8).

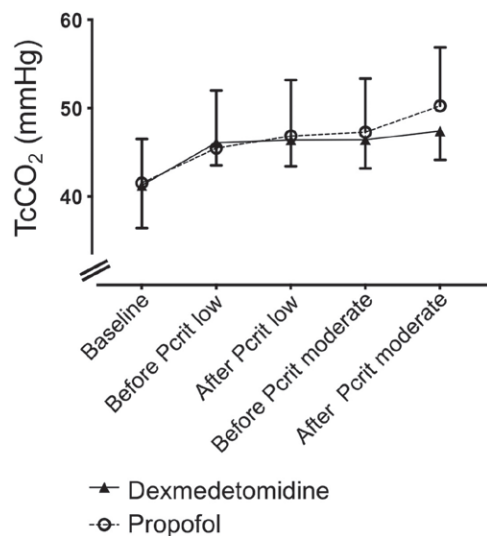
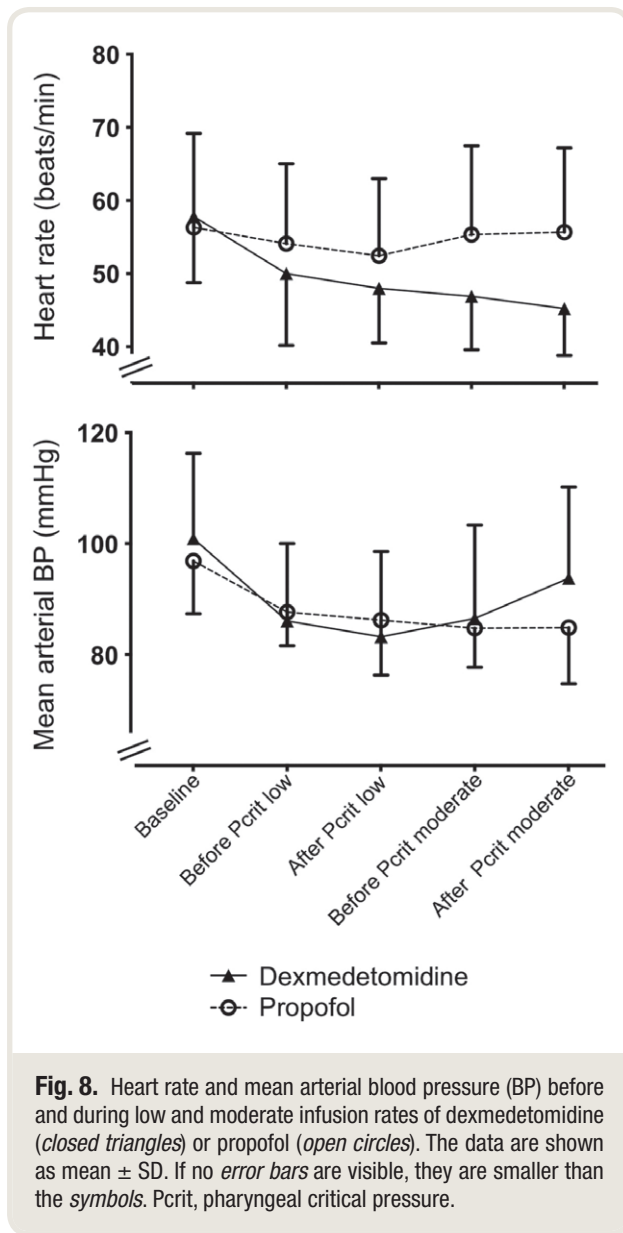


Fig. 7. Transcutaneous carbon dioxide (Tc CO_2) before and during low and moderate infusion rates of dexmedetomidine (closed triangles) or propofol (open circles). The data are shown as means \pm SD. If no error bars are visible, they are smaller than the symbols. Pcrit, pharyngeal critical pressure.

Discussion

A difference in upper airway collapsibility during dexmedetomidine and propofol sedation was not observed in this study, regardless of level of sedation. Importantly, we observed pharyngeal critical pressure values indicative of total obstruction at atmospheric pressure (*i.e.*, pharyngeal critical pressure values of at least 0 cm H_2O) in five of the nine subjects during dexmedetomidine infusion at low and/or moderate infusion rates, which is contrary to previous assertions that this drug protects against such obstruction.⁷⁻⁹ Furthermore, the same five subjects were the only subjects to exceed this 0 cm H_2O threshold during propofol sedation at low and/or moderate infusion rates. Correlation analysis confirmed a strong relationship in pharyngeal critical pressure between both drugs and at both infusion rates. Moreover, induction of sedation was associated with prolonged apneas in three of the nine subjects with either drug, suggesting similar effects of the two drugs on ventilatory drive.



Dexmedetomidine is increasingly used for sedation in both children and adults, with and without obstructive sleep apnea, in the belief that both upper airway patency and ventilatory drive are less compromised than with other sedative agents.²² With these purported benefits, its use for drug-induced sedation endoscopy as a diagnostic tool for identifying the level of airway obstruction during sleep is being increasingly advocated.²³ However, systematic evaluation of drug-induced sedation endoscopy during propofol *versus* dexmedetomidine sedation has identified no differences in airway obstruction in terms of anatomical location (velum, oropharyngeal lateral walls, tongue base, and epiglottis) and severity (none, partial, or complete) between the sedative agents during both light (Bispectral Index score of 65 to 75) and deep (Bispectral Index score of less than

60) sedation.^{10,24,25} These findings and those of the present study seriously question the assumption that dexmedetomidine, when used for sedation, has minimal adverse effect on airway stability.

Consistent with the findings of the present study and one we previously conducted,¹² magnetic resonance imaging demonstrates that dexmedetomidine sedation is associated with reductions in upper airway dimensions in healthy children,¹¹ although clinically significant airway obstruction was not observed. However, in two other studies comparing upper airway behavior during dexmedetomidine and propofol sedation for magnetic resonance imaging in children with obstructive sleep apnea, there was a need for an artificial airway or airway maneuvers in 14% and 11% of children sedated with dexmedetomidine *versus* 40% and 23%, respectively, when propofol was used.^{26,27}

The range of upper airway collapsibility seen in our participants reflects that seen in the general community.^{20,28} We observed similarities in airway behavior between dexmedetomidine and propofol sedation across this range of individual collapsibility (fig. 5). However, we did not study patients with difficult airways specifically. Although it is possible that the airway behavior of individuals with difficult airways could be different, there is no indication of this from the data of those with more collapsible airways in our study (fig. 5).

Contrary to previous studies of pharyngeal critical pressure during propofol sedation, the pharyngeal critical pressure level did not consistently increase with a deeper level of sedation with either drug,^{2,13} although we did not explore as deep levels of sedation in the present study. The relatively stable pharyngeal critical pressure levels observed here may reflect the relatively profound muscle deactivation that accompanies the transition from wakefulness to unconsciousness, leaving little room for further change.² Indeed, although previous studies have demonstrated a dose effect with propofol, the increase in pharyngeal critical pressure values with increased effect site concentrations was relatively small.^{2,13}

Although both drugs have powerful sedative effects, dexmedetomidine, a noradrenergic drug, and propofol, a γ -aminobutyric acid-mediated drug, have different molecular targets within the brain. In producing sedation, dexmedetomidine inhibits stimulatory pathways, whereas propofol activates inhibitory ones, each molecular target having different structural correlates within the brain.^{5,6,29} It may be that these different actions result in differences in other characteristics that could influence upper airway behavior and protection from upper airway collapse, such as their effects on arousal thresholds with, perhaps, a readier tendency to arouse from obstructive events with dexmedetomidine than with propofol. In this regard, it is of interest to note the different relationships between infusion rates and depth of sedation between the two drugs evident in figure 4. With propofol, there is a progressive increase in depth of sedation

assessed both objectively (Bispectral Index score) and subjectively (sedation scales), whereas with dexmedetomidine, there appears to be a plateauing of effect with less change in sedation levels between low and moderate infusion rates than between the wake baseline and low infusion rate. This suggests a wider therapeutic index with dexmedetomidine sedation than with propofol sedation. It should be noted that in our assessment of arousal thresholds, we were careful to minimize environmental disturbance, which included limiting the number of arousals inducing sedation checks; hence, the relative stability of sedation with each drug was not formally assessed.

It was notable that, in addition to their effects on airway collapsibility, other aspects of breathing behavior were similarly affected by the two drugs. The three subjects who experienced persistent central apneic events (prolonged pauses in respiratory effort) during induction of sedation did so with both drugs, although the effect appeared to be a little more amplified with dexmedetomidine. Although the reason for these pauses is not entirely clear, our observations are in line with previous findings of irregular breathing and apnea that have been reported during administration of both dexmedetomidine^{7,12} and another $\alpha 2$ -adrenoceptor agonist, clonidine.^{30–32} $\alpha 2$ -Adrenoceptors are widely distributed in the central nervous system including brainstem sites associated with respiratory control. $\alpha 2$ -Adrenergic agonists have been shown to reduce the firing rate of neurons and cause disturbances in respiratory pattern not dependent on the carotid body, suggesting an effect on central $\alpha 2$ -adrenoceptors that affects the rhythm of breathing.^{33,34} It is also possible that these apneic periods may represent perturbations in ventilation that accompany changes in the apneic threshold for hypercapnic ventilatory drive that accompanies loss of consciousness with sleep or sedation, which can vary between individuals.³⁵ Regardless of the mechanism, transcutaneous carbon dioxide increased to a similar degree with sedation with both drugs, suggesting a similar overall ventilatory depressant effect.

There are several limitations to this study. First, there was a small number of participants, reflecting the commitment required of them and the complexity of the study. Given the low numbers involved, although we failed to demonstrate a difference in airway collapsibility between the drug regimens, this does not equate to confirmation of equivalence. However, there were sufficient subjects to demonstrate that dexmedetomidine sedation is associated with substantial airway collapsibility in some of them and that the degree of collapsibility observed is related to that seen with propofol at equivalent infusion rates. These findings are contrary to the widely held belief that the upper airway is less vulnerable to obstruction during dexmedetomidine sedation than during sedation with propofol. Second, the variability in collapsibility between subjects potentially complicated interpretation given the small number involved. A difference in upper airway collapsibility between the two drugs

may exist, but to detect this, a study with much greater sample sizes would be necessary. However, the observed variability can also be regarded as strength because it reflects the variability found in the general population. Third, our use of a set infusion rate for administration of the sedative agent, which was done to standardize conditions as much as possible, resulted in different sedation levels, as reflected by Bispectral Index scores and sedation scales, between the agents and across the subjects. Adding to this, the Bispectral Index score is not validated for dexmedetomidine, and earlier studies have shown that the Bispectral Index score at equal clinical levels of sedation tends to be lower for dexmedetomidine than for propofol.³⁶ However, comparison of collapsibility at both these prescribed infusion rates and at nearly equivalent levels of sedation demonstrated a similar effect on upper airway collapsibility. Nonetheless, a more pronounced effect on airway collapsibility during dexmedetomidine sedation at an infusion rate increased to produce an equivalent sedation level to that induced by moderate propofol infusion cannot be ruled out. Last, the study was not conducted in a blinded fashion and was therefore susceptible to bias during data collection and analysis. Blinding during data collection would have been possible although challenging because of the different appearance of the study drugs. Blinding during analysis would have also been possible with a larger research team.

Strengths of the study are a careful experimental setup designed to evaluate upper airway collapsibility directly that is well validated in several previous studies^{1,2,13,17,21} and the use of propofol, a sedative drug that is well characterized regarding upper airway collapsibility, as a direct comparator in a crossover design, *i.e.* the same individuals were tested with both drugs. In addition, drug concentrations in plasma were quantified as an objective indirect measure of sedation, and the concentration results indicated that light to moderate levels of sedation were achieved.^{6,8,36,37}

Conclusions

Upper airway collapsibility is similar during dexmedetomidine and propofol sedation, questioning the belief that dexmedetomidine offers protection against upper airway obstruction relative to sedation with this other commonly used anesthetic agent. Episodes of clinically significant apnea can occur during induction of sedation with both drugs.

Acknowledgments

The authors thank Vanessa Baker, B.Sc., Kelly Shepherd, Ph.D., West Australian Sleep Disorders Research Institute, Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, and Katariina Jarvi, M.D., Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, for assistance in conduction of the trial; Celeste Wale, B.Sc. (hons), and Dijana Tesic, B.Sc.

(hons), School of Human Sciences, University of Western Australia, Perth, Western Australia, for managing blood samples; Anette Ebberyd, B.M.A., and Souren Mkrtchian, M.D., Ph.D., Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden, for analysis of plasma concentrations of propofol; Saija Sirén, M.Sc., University of Turku, Turku, Finland, for dexmedetomidine concentration analysis; and Eva Hagel, M.S.Sc, Medical Statistics Unit, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden, for statistical support.

Research Support

This work was supported by the departments and institutions involved; by grants from the Stockholm County Council; and by funds from the Karolinska Institutet, Stockholm, Sweden (to Dr. Fagerlund); and by project grant No. 16-030 from the Australian and New Zealand College of Anaesthetists. Travel grants were received from the Swedish Society of Medicine, the Erik and Edith Fernström Foundation for Medical Research, and the Olof Norlander Memorial Fund, Stockholm, Sweden (to Dr. Lodenius). This work was also supported in part by a National Health and Medical Research Council senior research fellowship (No. 1042341; to Dr. Eastwood).

Competing Interests

Dr. Eriksson received lecture fees from Merck Inc. Sweden (Stockholm, Sweden) and is a medical advisor to Saniona A/S (Copenhagen, Denmark). Dr. Scheinin has contract research relationships with Orion Corporation (Espoo, Finland); AstraZeneca (Espoo, Finland); Hoffmann–La Roche (Espoo, Finland); Novartis (Espoo, Finland); and AC Immune SA (Lausanne, Switzerland). Dr. Scheinin has also received speaker's fees and research support from Orion Corporation and speaker's fees from Pharma Industry Finland (Helsinki, Finland). Drs. Maddison, Eastwood, Hillman, and Walsh have contract research relationships with Zeldia Therapeutics Pty Ltd. (Perth, Australia); Nyxoah S.A. (Mont-Saint-Guibert, Belgium); and Oventus (Indooroopilly, Australia). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: Ase.Lodenius@remeoclinic.se. Raw data available at: Ase.Lodenius@remeoclinic.se.

Correspondence

Address correspondence to Dr. Lodenius: DESA, Remeo, R-kliniken AB, Thorsten Levenstams väg 4, 128 64 Sköndal, Sweden. Ase.Lodenius@remeoclinic.se. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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