

## Dexmedetomidine Pharmacodynamics: Part I

### Crossover Comparison of the Respiratory Effects of Dexmedetomidine and Remifentanyl in Healthy Volunteers

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**Background:** Dexmedetomidine, a highly selective  $\alpha_2$ -adrenoceptor agonist used for short-term sedation of mechanically ventilated patients, has minimal effect on ventilation.

**Methods:** This study compared the respiratory effect of dexmedetomidine to that of remifentanyl. The authors measured and compared respiratory responses of six healthy male volunteers during (1) a stepwise target-controlled infusion of remifentanyl, (2) a stepwise target-controlled infusion of dexmedetomidine, and (3) a pseudonatural sleep session.

**Results:** Compared with baseline, remifentanyl infusions resulted in respiratory depression as evidenced by a decrease in respiratory rate and minute ventilation, respiratory acidosis, and apnea episodes resulting in desaturations. Remifentanyl disturbed the natural pattern of breathing and flattened the distribution of ventilatory timing (inspiratory time/ventilatory cycle time). The respiratory effects of dexmedetomidine markedly contrasted with those of remifentanyl. When compared with baseline, during dexmedetomidine infusions, the respiratory rate significantly increased, and the overall apnea/hypopnea index significantly decreased. The distribution of inspiratory time/ventilatory cycle time showed an increased peak. In addition, dexmedetomidine seemed to mimic some aspect of natural sleep. While the subjects were breathing a 5% CO<sub>2</sub> mixture, hypercapnic arousal phenomena (documented by the Bispectral Index, the electroencephalogram, and sudden increase in the minute ventilation) were observed during dexmedetomidine infusions. Similar phenomena during natural sleep have been reported in the literature.

**Conclusions:** In comparison with remifentanyl, dexmedetomidine infusions (1) did not result in clinically significant respiratory depression, (2) decreased rather than increased the apnea/hypopnea index, and (3) exhibited some similarity with natural sleep.

RESPIRATORY depression is a concern when using potent analgesics or sedatives.<sup>1</sup> Routine use of sedatives such as midazolam can lead to a fatal outcome when overdosed.<sup>2</sup> Dexmedetomidine, a highly selective  $\alpha_2$ -adrenoceptor agonist, is currently used for short-term sedation of initially intubated and mechanically ventilated patients. A high concentration of  $\alpha_2$  receptors is found in the locus ceruleus,<sup>3</sup> which is involved in regulating sleep and may be involved in the modulation of the respiratory controls.<sup>4,5</sup> Dexmedetomidine, through its actions on the  $\alpha_2$  adrenoceptors, imparts sedative and analgesic effects while having minimal ventilatory effects.<sup>6</sup>

The respiratory safety of dexmedetomidine has been suggested by three studies.<sup>6-8</sup> Although Ebert *et al.*<sup>6</sup> investigated dexmedetomidine infusions over a wide range of concentrations, their respiratory data are limited to respiratory rate and blood gases. Belleville *et al.*<sup>7</sup> presented a more elaborate respiratory analysis, but their study was limited to relatively small boluses of dexmedetomidine, and the plasma concentrations were not measured. Finally, Venn *et al.*<sup>8</sup> performed a retrospective analysis of the respiratory rate and blood gas data from surgical patients in the surgical intensive care unit.

We designed this study to further characterize the respiratory and analgesic effects of dexmedetomidine over a wide range of plasma concentrations. The analgesic and respiratory depressant effects of opioids are well characterized.<sup>9</sup> Therefore, to validate our methods and provide a clinical point of reference to the effects measured with dexmedetomidine, we compared the pharmacodynamic effects of dexmedetomidine to remifentanyl, a very short-acting opioid. We measured and compared respiratory, analgesic, and sedative responses of healthy male volunteers during (1) a stepwise target-controlled infusion (TCI) of remifentanyl, (2) a stepwise TCI of dexmedetomidine, and (3) a pseudonatural sleep session. This article focuses on the respiratory effects of dexmedetomidine, whereas a companion manuscript examines its analgesic properties.

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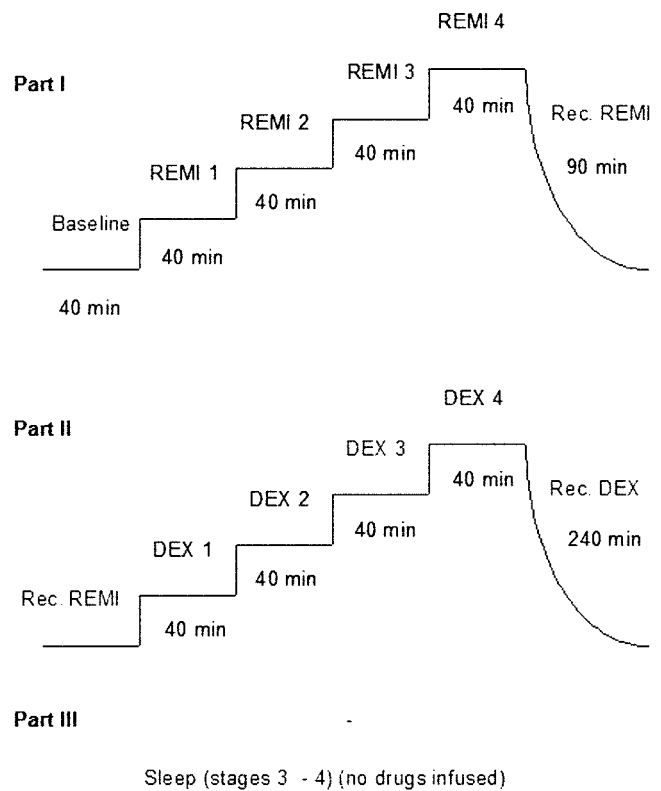
## Materials and Methods

### *Institutional Review Board and Inclusion/Exclusion Criteria*

After this study was approved by the Institutional Review Board (Duke University Medical Center, Durham, North Carolina), signed informed consent was obtained from each study subject. Eight male subjects, aged 21–40 yr, with American Society of Anesthesiologists physical status I, were enrolled. Subjects with a history of drug, tobacco, or alcohol abuse; chronic use of medications; gastroesophageal reflux; anticipated difficult airway; body mass index of less than 18 or greater than 28 kg/m<sup>2</sup>; or the presence of a beard or physiognomies precluding a good fit of a facemask were excluded. The subjects underwent a screening session during which a physical examination, a medical history, electrocardiography, and laboratory tests were performed. During the screening session, the subjects were familiarized extensively with the study procedures, monitoring devices were applied, and subjects rested supine with a tight-fitting mask strapped to their faces for a minimum of 30 min. A carbon dioxide challenge was also performed during the screening.

### *Conduct of the Study*

The protocol consisted of three parts, lasting more than 24 h (fig. 1). During parts 1 and 2, the subjects received remifentanyl or dexmedetomidine, respectively, *via* TCI. During part 3, no drugs were infused, and the subjects were requested to sleep. Because there were measurable residual concentrations of dexmedetomidine during part 3, the sleep during that part is referred to as *pseudonatural sleep*. During parts 1 and 2, the stepwise infusions were designed to target and maintain remifentanyl or dexmedetomidine plasma concentrations at four sequentially increasing steps. Each step lasted 40 min. Steps 1–4 targeted remifentanyl (part 1) plasma concentrations of 1, 2, 3, and 4 ng/ml and dexmedetomidine (part 2) plasma concentrations of 0.6, 1.2, 1.8, and 2.4 ng/ml. Remifentanyl plasma concentrations were chosen (from clinical experience) to be high enough to produce respiratory depression without inducing apnea, whereas dexmedetomidine plasma concentrations were chosen to range from a therapeutic level to supratherapeutic levels. The first step of dexmedetomidine (0.6 ng/ml) is a typical level used for sedating patients in the surgical intensive care unit. During part 1, at the end of step 4, the remifentanyl infusion was stopped, and a 90-min recovery period was allowed before starting part 2 to ensure that the subject returned to baseline.<sup>10</sup> Similarly, the dexmedetomidine infusion was stopped, during part 2 at the end of step 4, and, because the pharmacokinetics of dexmedetomidine is slower than that of remifentanyl, a 240-min recovery period was allowed before starting part 3 (fig. 1).<sup>11,12</sup>



**Fig. 1. Schematic of the protocol design.** DEX = dexmedetomidine; Rec. = recovery from; REMI = remifentanyl.

One of the eight subjects received a placebo instead of remifentanyl, and another subject received a placebo instead of dexmedetomidine. This was randomly assigned, and the investigators were blinded to it. The two placebo subjects were excluded from the respiratory analysis to perform a crossover comparison. The stopping criteria for both drug infusions were the following: a 40% change in the baseline mean arterial pressure, a mean arterial pressure of 50 mmHg or less for 3 min, a heart rate of 40 beats/min or less for 3 min, or respiratory depression necessitating assisted ventilation to maintain an oxygen saturation measured by pulse oximetry of 90% or greater.

The subjects fasted for 8 h before the study and were asked to abstain from caffeine and alcohol consumption for the preceding 24 h. On arrival in the morning, an 18-gauge intravenous cannula was inserted, and lactated Ringer's solution was infused at 100 ml/h. A 20-gauge catheter was inserted into the radial artery of the non-dominant hand. The subjects received 30 ml oral sodium citrate, 10 mg intravenous metoclopramide, and 50 mg intravenous ranitidine to minimize the risk of pulmonary aspiration. Nine gold cup electroencephalographic electrodes (C3, C4, F7, F8, Cz, Cz prime, A1, A2, and inion) were attached with collodion using standard sleep laboratory techniques. A three-lead electrocardiogram, a non-invasive blood pressure cuff, pulse oximeter probes, and

Respirace (Non-Invasive Monitoring Systems Inc., North Bay Village, FL) bands were also applied.

A three-way stopcock was used to allow subjects to breathe either 50% oxygen from a Venturi system or 5% CO<sub>2</sub> in 50% O<sub>2</sub> and 45% N<sub>2</sub> from the prefilled Douglas bag during the carbon dioxide challenge. The Douglas bag, connected to the carbon dioxide mixture cylinder, could be refilled as needed. The respiratory variables were measured continuously from a pneumotach, a capnograph, and the Respirace (respiratory inductive plethysmograph that monitors changes in lung volume).<sup>13</sup>

After all of the monitors were placed and the facemask was carefully adjusted, the lights were dimmed, and the subject was requested to rest quietly in the bed in the decubitus position for 30–60 min. The protocol was then initiated with baseline measurements.

### Measurements

At the beginning of each step, an infusion of the test drug (TCD) was initiated. A 5-min period was then allowed for equilibrium between the plasma and effect sites. Subjects were then kept undisturbed for an additional 5 min to collect electroencephalographic data. A 6-min carbon dioxide challenge was then performed, followed by sedation and pain assessments before repeating the carbon dioxide challenge (fig. 2). The second carbon dioxide challenge was performed to detect a possible effect of the pain assessment's stimulation on the hypercapnic ventilatory response (HCVR). During baseline, while no drug was infused, an identical procedure was performed.

At each step, the sedation was assessed using a visual analog scale,<sup>14</sup> the Ramsay score,<sup>15</sup> and the Observer's Assessment of Alertness/Sedation sum.<sup>16</sup> Blood samples were collected for pharmacokinetic analysis at 15 and 40 min of each step.

Before the beginning of each carbon dioxide challenge, the minute ventilation (MV) was averaged over 1 min, and an arterial blood gas (ABG) measurement was obtained. The three-way stopcock was then turned in position to allow the subject to breathe the 5% CO<sub>2</sub> mixture from the Douglas bag for 6 min.<sup>17,18</sup> The MV was averaged during the last minute of the carbon dioxide challenge, and another ABG was obtained before the three-way stopcock was turned back in position to allow the subject to breathe the 50% O<sub>2</sub> mixture in nitrogen. For each carbon dioxide challenge, the breath-to-breath MV was plotted in function of time, and a monoexponential model was fitted to the data. The monoexponential fit was used to compute how far the MV responses were from steady state (percent of the maximum predicted response).

The respiratory data were also analyzed during the 5-min epoch of electroencephalographic data collection to ensure an undisturbed breathing pattern. The variables analyzed included the following: end-tidal carbon

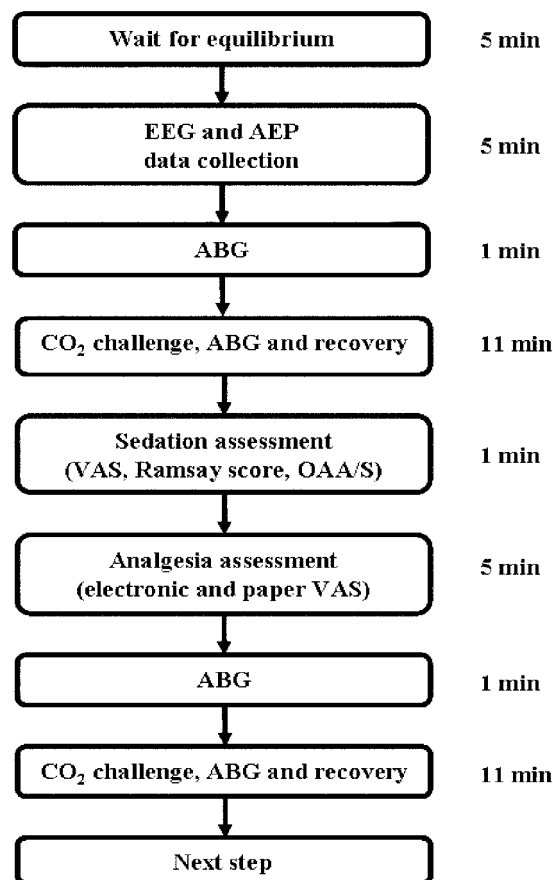


Fig. 2. Sequence of data collection during each 40-min step. ABG = arterial blood gas; AEP = auditory evoked potentials; CO<sub>2</sub> = carbon dioxide; EEG = electroencephalogram; OAA/S = Observer's Assessment of Alertness/Sedation; VAS = visual analog scale.

dioxide (ETCO<sub>2</sub>), tidal volume (V<sub>T</sub>), MV, ventilatory cycle time (Tt), inspiratory time (Ti), expiratory time, respiratory rate (RR), rib cage contribution, and oxygen saturation (SaO<sub>2</sub>).

The average MV was calculated from the sum of the tidal volumes of every breath in a 5-min epoch. The average Tt was computed by dividing the duration of the epoch by the number of breaths taken in that interval. The average Ti was computed by dividing the sum of the Ti by the number of breaths in that epoch. The capnograph data were analyzed using the average ETCO<sub>2</sub> in the minute preceding every ABG.

The drive V<sub>T</sub>/Ti (mean inspiratory flow) and timing Ti/Tt components of ventilation<sup>19</sup> were also recorded for each breath. The advantage of analyzing respiratory data in terms of V<sub>T</sub>/Ti and Ti/Tt resides in the fact that these parameters have been shown to be physiologically independent<sup>19</sup> one from another, while

$$MV = V_T/Ti \times Ti/Tt.$$

The breath-by-breath Ti/Tt and V<sub>T</sub>/Ti values of the six subjects were used to construct histograms of their distribution at each step.



Breathing patterns were monitored continuously using the RespiTrace. The software RespiEvents (Non-Invasive Monitoring Systems Inc.) was used to classify all apnea events into one of two categories, either central or obstructive, and to compute the apnea/hypopnea index (AHI). An apnea event was defined as an absence of tidal volume for at least 10 s in duration. A hypopnea event was defined as tidal volumes smaller than 25% of the baseline tidal volume for at least 10 s in duration. The AHI is defined as the number of apnea and hypopnea events per hour. At each step, the subjects were classified as having significant apnea ( $AHI \geq 15$ ) or not having significant apnea ( $AHI < 15$ ).

During the overnight portion of the study, while the subjects were sleeping without any drug being infused, the stages of sleep were assessed using continuous electroencephalographic monitoring. The respiratory pattern was analyzed throughout the night, whereas the carbon dioxide challenges were performed during slow-wave sleep stages (stages 3 and 4).<sup>20</sup>

#### Monitoring and Equipment

The following monitoring equipment was used: Spacelabs 90603a (SpaceLabs Medical Products, Redwood, WA) for the electrocardiogram and invasive arterial blood pressure; Dinamap (Critikon, Tampa, FL) for noninvasive blood pressure; Ohmeda 5200 capnograph (Datex-Ohmeda Inc., Louisville, CO); Bicore CP-100 pneumotach (Bear Medical Systems Inc., Riverside, CA); Biox 3700 pulse oximeter; respiratory inductive plethysmography RespiTrace 204 (Non-Invasive Monitoring Systems Inc.)<sup>13</sup>; and A-1000 four-channel electroencephalograph and Bispectral Index<sup>®</sup> (BIS<sup>®</sup>) monitor (Aspect Medical Systems Inc., Framington, MA). The respiratory equipment (Hans Rudolph, Inc., Kansas City, MO) included a 1-l calibrating syringe, a Douglas bag, nonbreathing circuit and low-resistance valve, a three-way low-resistance stopcock, and a tight-fitting facemask. The data from the electronic monitoring equipment (including raw electroencephalograph, digitized at 128 Hz) were downloaded each second to a LabView data acquisition system (version 6.0; Labview, Austin, TX).

Arterial blood gases were analyzed with the VIA-ABG (VIA Medical Corporation, San Diego, CA). The TCI pump devices consisted of two laptop computers connected to infusion pumps (Harvard Pump 22; Harvard Apparatus, South Natick, MA). STANPUMP\*\* was used to run the TCI pumps. The pharmacokinetic parameters used for the infusions of remifentanyl and dexmedetomidine were those published by Minto *et al.*<sup>21</sup> and Dyck *et al.*,<sup>11</sup> respectively.

#### Calibration

Before each experiment, the VIA-ABG monitor was calibrated according to the manufacturer's specification; the capnograph calibration was verified at room air using a 5% CO<sub>2</sub> mixture; and the Bicore pneumotach calibration was verified with the 1-l calibration syringe. The RespiTrace was calibrated by qualitative diagnostic calibration (*i.e.*, self-calibration)<sup>22</sup> when subjects had been undisturbed and breathing at rest for 5 min. The drift of the RespiTrace was minimized by turning on the monitor 3 h before the start of the study<sup>13</sup> and by recalibrating the monitor before each of the three parts of the protocol.

#### Statistical Analysis

A paired Student *t* test with a Bonferroni correction was used for comparing continuous data involving three groups. For continuous data involving more than three groups, intergroup and intragroup comparisons were analyzed using analysis of variance, with the Dunnett method used for multiple comparisons.<sup>23</sup> Contingency tables were analyzed using chi-square tests. Data are reported as mean  $\pm$  SD or median (range), depending on the pattern of distribution. *P* values less than 0.05 were considered statistically significant. Histograms were constructed to visually assess the single-breath distributions of the timing and drive components of ventilation  $T_i/T_t$  and  $V_T/T_i$ . The software programs S-plus 6.0 (Insightful Corp, Seattle, WA) and JumpIn (SAS Institute Inc., Cary, NC) were used for the statistical analyses.

## Results

#### Pharmacokinetics

Plasma concentrations of remifentanyl and dexmedetomidine are summarized in table 1. For both remifentanyl and dexmedetomidine, there were no statistical differences between the first and second samples drawn within each step, showing that a stable level was achieved at each step.

#### Sedation

As shown in figure 3, the subjects were minimally sedated during remifentanyl infusions. During dexmedetomidine infusion steps 1 and 2, the subjects were sedated and arousable. In contrast, during steps 3 and 4, deeper levels of hypnosis were attained, and most subjects were completely unarousable.

#### Hemodynamics

As shown in tables 2 and 3, remifentanyl infusions had no effect on mean arterial pressure and heart rate, whereas higher concentrations of dexmedetomidine resulted in a statistically significant increase in mean arterial pressure and decrease in heart rate.

\*\* STANPUMP copyright S. L. Shafer, Palo Alto Department of Veterans Affairs Medical Center, Palo Alto, California; software available at <http://anesthesia.stanford.edu/pkpd/>. Accessed September 19, 2004.

**Table 1. Summary of the REMI and DEX Plasma Concentrations**

Remifentanyl		Dexmedetomidine	
Target Plasma Concentrations, ng/ml	Measured Plasma Concentrations, ng/ml	Target Plasma Concentrations, ng/ml	Measured Plasma Concentrations, ng/ml
1.0	0.83 (0.21)	0.6	0.65 (0.07)
	0.74 (0.21)		0.69 (0.08)
2.0	1.42 (0.33)	1.2	1.64 (0.18)
	1.86 (0.48)		1.79 (0.16)
3.0	2.34 (0.45)	1.8	2.90 (0.28)
	2.32 (0.52)		2.71 (0.09)
4.0	3.01 (1.20)	2.4	3.74 (0.43)
	3.38 (1.51)		3.85 (0.33)
Recovery 30 min after termination of remifentanyl infusion	0 (0)		

Values are presented mean  $\pm$  SD. For each step, the first and second values are for the first and second PK samples collected within each step, respectively.

### Hypercapnic Ventilatory Response

On average, 91% of the maximum predicted MV response was achieved within 6 min (SD = 10.9%), and 75% of the challenges reached 86% of the maximum predicted response or greater. Most of the challenges with no drugs reached stable MV. The response of a typical subject, at different steps of the study, is shown in figure 4. At baseline, the  $ET_{CO_2}$  was rapidly stable, and the MV was relatively stable before the end of the carbon dioxide challenge. As the plasma concentration of remifentanyl increases, the breath-to-breath MV response flattened, and the  $ET_{CO_2}$  increased. By the last step of remifentanyl infusion, breathing was irregular with periods of apnea, while the  $ET_{CO_2}$  markedly increased. After cessation of the remifentanyl infusion (recovery), the MV response and  $ET_{CO_2}$  returned almost completely to baseline. During dexmedetomidine infusions, both the  $ET_{CO_2}$  and MV responses were relatively preserved and similar to the baseline and recovery.

Although the MV responses during baseline and recovery mostly followed an exponential and smooth increase (fig. 4), they were often irregular with sudden dramatic changes in MV during dexmedetomidine infusions (figs. 5A and B), as if the subject was being aroused. The plots of the BIS values (fig. 5) confirm this impression. During the carbon dioxide challenges exhibiting sudden changes in MV, the BIS values correlate closely with MV (figs. 5A and B). Conversely, during the carbon dioxide challenges exhibiting a smooth exponential response, the BIS values showed no correlation with the MV (fig. 5C). Because two recent articles suggested that BIS values might track muscle activity,<sup>24,25</sup> we plotted the raw electroencephalographic signals, which confirmed that BIS was indeed detecting a true arousal phenomenon rather than a muscle artifact (fig. 6).

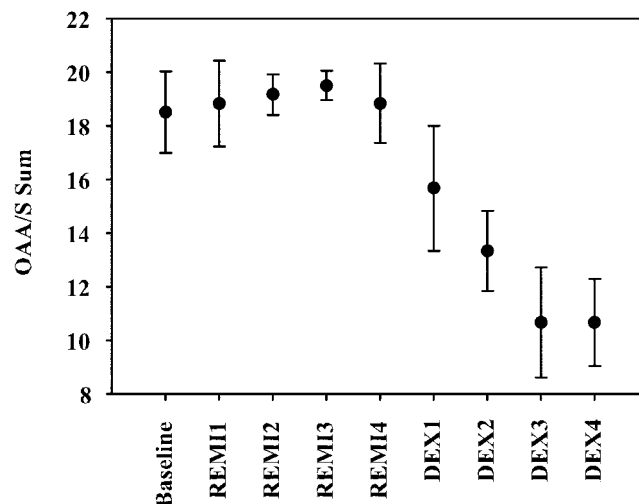
The changes in arterial carbon dioxide tension ( $P_{aCO_2}$ ) and in MV during the HCVRs are summarized in table 4. A statistical analysis was performed by comparing to the baseline the change in  $P_{aCO_2}$  and the change in MV during the remifentanyl, recovery, and dexmedetomidine phases. Each of the four steps of remifentanyl infusions resulted in a statistically significant decrease in the change in MV when compared with baseline. No significant changes were observed during the recovery or dexmedetomidine steps.

### Respiratory Pattern Analysis (Respirace)

During remifentanyl infusions, decreases in MV and  $Ti/Tt$ , consistent with respiratory depression, were observed (table 2). In contrast, during dexmedetomidine infusions, an increased RR and a decreased  $Tt$ , consistent with an absence of respiratory depression, were observed (table 3). MV,  $Ti/Tt$ , RR, and  $Tt$  returned to their baselines after recovery from remifentanyl and dexmedetomidine.

Central apnea was observed during remifentanyl infusions, during the pseudonatural sleep part, but not during dexmedetomidine infusions. The frequency of these episodes (expressed in number of events per hour as median and range) were 3 (0-7) during remifentanyl and 0 (0-3) during sleep. Episodes of obstructive apnea were observed during all three parts.

The AHI (tables 2 and 3) was analyzed using the chi-square test on the pooled data for remifentanyl and dexmedetomidine. Remifentanyl infusions increased the likelihood of observing AHIs greater than 15, compared with the likelihood of observing AHIs greater than 15 during baseline, remifentanyl recovery, and sleep stages ( $P < 0.05$ ). In addition, during remifentanyl infusions, two subjects had episodes of prolonged (60-90 s) apnea



**Fig. 3.** The Observer's Assessment of Alertness/Sedation scale (OAA/S) sum in function of the step. The scale ranges from 9 (completely unresponsive) to 20 (awake and not sedated). DEX = dexmedetomidine; REMI = remifentanyl.

**Table 2. Breathing Pattern Variables during Part 1**

	Baseline	REMI1	REMI2	REMI3	REMI4
Ti/Tt	0.39 ± 0.08	0.29 ± 0.10	0.30 ± 0.11	0.28 ± 0.09	0.25 ± 0.10*
V <sub>T</sub> /Ti, ml/s	310 ± 65	266 ± 48	334 ± 113	368 ± 87	425 ± 222
V <sub>T</sub> , ml	616 ± 224	450 ± 103	636 ± 247	578 ± 145	788 ± 433
RC, %	37.2 ± 4.9	44.3 ± 6.0	53.1 ± 11.6	50.3 ± 12.9	53.3 ± 14.2*
Tt, s	5.4 ± 2.3	6.6 ± 2.1	7.3 ± 3.0	6.1 ± 1.6	7.5 ± 2.2
MV, ml/min	6,994 ± 1,984	4,379 ± 1,982*	4,713 ± 1,270	5,419 ± 1,336	4,514 ± 1,325*
RR, breaths/min	12.1 ± 4.3	9.5 ± 4.8	8.2 ± 4.1	9.1 ± 3.1	6.8 ± 3.4
pH	7.42 ± 0.01	7.39 ± 0.02	7.37 ± 0.03	7.34 ± 0.04*	7.32 ± 0.04*
Paco <sub>2</sub> , mmHg	39.9 ± 2.7	44.6 ± 3.3	47.8 ± 5.9	52.3 ± 6.5*	55.3 ± 8.4*
PaO <sub>2</sub> , mmHg	231.7 ± 33.4	194.6 ± 35.8	204.9 ± 55.2	166.2 ± 52.8	173.2 ± 57.8
SaO <sub>2</sub> , %	99.1 ± 0.2	99.1 ± 0.2	98.5 ± 1.7	98.3 ± 1.0	97.3 ± 2.7
BE, mEq/l	0.0 ± 1.2	1.7 ± 1.3	2.3 ± 1.7	2.3 ± 1.1	2.1 ± 1.1
HCO <sub>3</sub> , mEq/l	24.4 ± 1.1	26.8 ± 1.3	27.5 ± 1.3*	28.1 ± 1.3*	28.2 ± 1.6*
ETco <sub>2</sub> , mmHg	35.5 ± 3.5	38.1 ± 6.9	43.4 ± 6.0	44.6 ± 11.3	46.3 ± 10.2
AHI > 15	3	3	4	4	5
HR, beats/min	64 ± 14	58 ± 14	60 ± 13	63 ± 12	63 ± 8
MAP, mmHg	87 ± 5	85 ± 11	86 ± 11	87 ± 10	88 ± 12

Values are presented as mean ± SD.

\*  $P < 0.05$  from baseline (analysis of variance and Scheffé *post hoc* testing).

AHI = apnea/hypopnea index; BE = base excess; ETco<sub>2</sub> = end-tidal carbon dioxide; HR = heart rate; MAP = mean arterial pressure; MV = minute ventilation; Paco<sub>2</sub> = arterial carbon dioxide tension; PaO<sub>2</sub> = arterial oxygen tension; RC = contribution of the ribcage; REMI = remifentanil; RR = respiratory rate; SaO<sub>2</sub> = arterial oxygen saturation; Ti/Tt = timing component of ventilation; Tt = respiratory cycle time; V<sub>T</sub> = tidal volume; V<sub>T</sub>/Ti = drive component of ventilation (mean inspiratory flow).

associated with desaturation (SaO<sub>2</sub> ≤ 80%) and were prompted to breathe. In contrast, dexmedetomidine infusions resulted in a significant decrease in the likelihood of observing AHIs greater than 15, compared to the likelihood of observing AHIs greater than 15 during baseline, remifentanil recovery, and sleep stages ( $P < 0.003$ ).

The distribution of breath-to-breath Ti/Tt pooled for each step is shown in figure 7. The Ti/Tt histograms flattened during remifentanil infusions and peaked during dexmedetomidine infusions when compared with

baseline. The histograms returned to baseline after recovery from remifentanil and dexmedetomidine.

#### ABG Analysis

The average levels of arterial oxygen tension (PaO<sub>2</sub>) and SaO<sub>2</sub> did not significantly change from baseline with either dexmedetomidine or remifentanil (tables 2 and 3). The ABG analyses performed during dexmedetomidine infusion were consistent with a well-compensated mild respiratory acidosis (table 3). The Paco<sub>2</sub> levels increased

**Table 3. Breathing Pattern Variables during Part 2**

	Baseline	DEX1	DEX2	DEX3	DEX4
Ti/Tt	0.39 ± 0.08	0.44 ± 0.05	0.48 ± 0.07	0.45 ± 0.05	0.45 ± 0.05
V <sub>T</sub> /Ti, ml/s	310 ± 65	292 ± 72	305 ± 135	342 ± 121	328 ± 95
V <sub>T</sub> , ml	616 ± 224	551 ± 136	491 ± 158	494 ± 177	461 ± 118
RC, %	37.2 ± 4.9	34.2 ± 18.0	41.2 ± 17.6	40.3 ± 31.2	37.2 ± 24.0
Tt, s	5.4 ± 2.3	4.3 ± 0.8	3.6 ± 0.5*	3.3 ± 0.3*	3.2 ± 0.3*
MV, ml/min	6,994 ± 1,984	7,054 ± 2,276	8,358 ± 2,863	9,432 ± 3,154	8,846 ± 1,998
RR, breaths/min	12.1 ± 4.3	13.1 ± 3.1	16.6 ± 3.5	19.0 ± 2.3*	19.2 ± 2.0*
pH	7.42 ± 0.01	7.40 ± 0.02	7.40 ± 0.01	7.38 ± 0.03*	7.40 ± 0.03
Paco <sub>2</sub> , mmHg	39.9 ± 2.7	45.1 ± 2.9	45.4 ± 3.5	47.5 ± 5.5	44.7 ± 5.1
PaO <sub>2</sub> , mmHg	231.7 ± 33.4	238.9 ± 26.1	228.0 ± 43.6	205.3 ± 53.9	211.5 ± 44.5
SaO <sub>2</sub> , %	99.1 ± 0.2	99.2 ± 0.3	99.0 ± 0.0	99.0 ± 0.3	99.2 ± 0.3
BE, mEq/l	0.0 ± 1.2	3.2 ± 1.9	3.1 ± 2.0	2.5 ± 2.5	2.4 ± 2.7
HCO <sub>3</sub> , mEq/l	24.4 ± 1.1	28.0 ± 1.9	27.9 ± 2.0	27.7 ± 2.5	27.3 ± 2.7
ETco <sub>2</sub> , mmHg	35.5 ± 3.5	39.2 ± 4.2	36.3 ± 2.8	38.2 ± 6.1	38.9 ± 4.2
AHI > 15	3	0	0	0	0
HR, beats/min	64 ± 14	62 ± 9	53 ± 9*	50 ± 13*	49 ± 10*
MAP, mmHg	87 ± 5	82 ± 6	87 ± 9	98 ± 7*	103 ± 7*

Values are presented as mean ± SD.

\*  $P < 0.05$  from baseline (analysis of variance and Scheffé *post hoc* testing).

AHI = apnea/hypopnea index; BE = base excess; DEX = dexmedetomidine; ETco<sub>2</sub> = end-tidal carbon dioxide; HR = heart rate; MV = minute ventilation; Paco<sub>2</sub> = arterial carbon dioxide tension; PaO<sub>2</sub> = arterial oxygen tension; RC = contribution of the ribcage; RR = respiratory rate; SaO<sub>2</sub> = arterial oxygen saturation; Ti/Tt = timing component of ventilation; Tt = respiratory cycle time; V<sub>T</sub> = tidal volume; V<sub>T</sub>/Ti = drive component of ventilation (mean inspiratory flow).

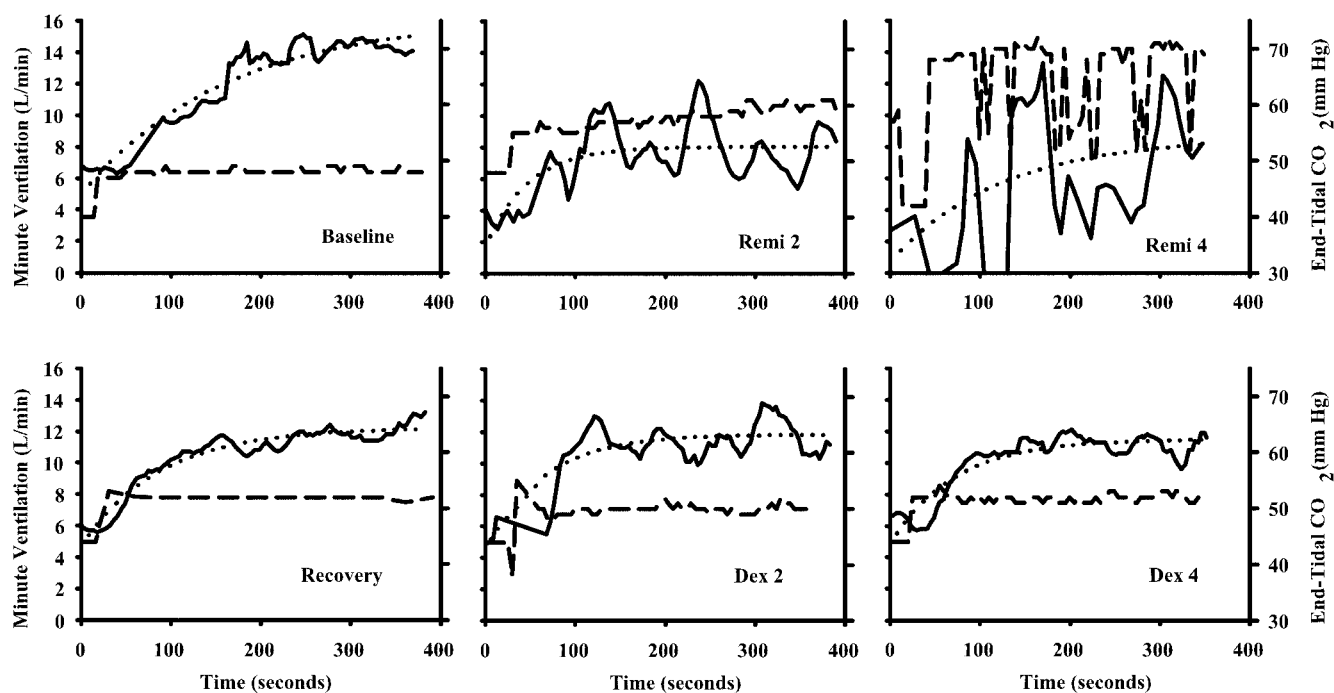


Fig. 4. Measurement of the hypercapnic ventilatory response of a typical subject. Carbon dioxide ( $\text{CO}_2$ ) was added at time = 0. The measured minute ventilation, predicted minute ventilation, and end-tidal carbon dioxide are, respectively, represented by the continuous, dotted, and dashed lines. BIS = Bispectral Index. See text for more detail.

during dexmedetomidine infusion but reached a plateau after step 1 (table 3). Conversely, with remifentanyl, we observed a pattern of moderate to severe respiratory acidosis with partial metabolic compensation (table 2). The  $\text{Paco}_2$  levels during remifentanyl infusion showed concentration-related increments (table 2).

#### Placebo and Recovery

Data from the two placebo subjects during placebo infusion were similar to their respective baselines. The data of the drug infusion part were consistent with the drug effects observed in the six nonplacebo subjects (data not shown). During recovery from remifentanyl and dexmedetomidine infusions, all measured variables returned to their baseline values (data not shown).

## Discussion

#### Pharmacokinetics and Sedation

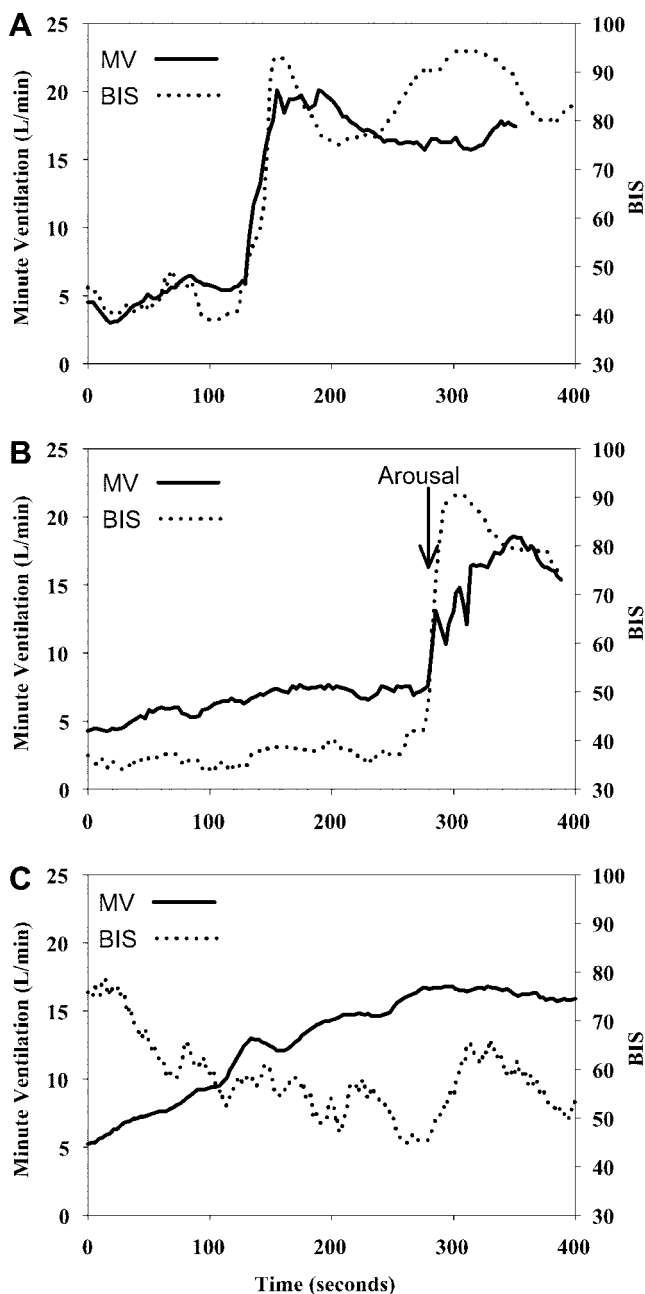
All of the subjects were easily arousable throughout the remifentanyl infusions. Dexmedetomidine infusions resulted in suprathreshold plasma concentrations. Dosing guidelines of dexmedetomidine for intensive care unit sedation target a plasma concentration of 0.6 ng/ml, which is equivalent to our first infusion step. During step 4, the average plasma concentration of dexmedetomidine was 3.78 ng/ml, which is three times higher than the plasma concentration (1.2 ng/ml) associated with the maximum dosing recommended in the package insert ( $0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). While subjects were

sedated but arousable during steps 1 and 2, deeper levels of hypnosis were attained during steps 3 and 4, and most subjects were completely unarousable.

#### Hypercapnic Ventilatory Response

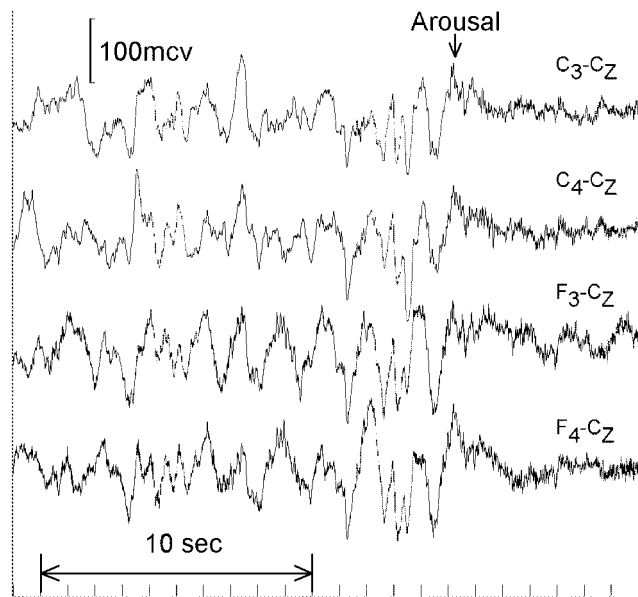
As expected, the HCVR response was significantly decreased during remifentanyl infusion. In contrast, the HCVR response did not change after dexmedetomidine infusions. However, as shown in figure 5, in some of the carbon dioxide challenges during dexmedetomidine infusions, the increase in MV coincided with arousal phenomenon. Such arousal phenomenon, secondary to the hypercapnia stimulation, has been described during natural sleep by Berthon-Jones and Sullivan,<sup>26</sup> and their numbers are strikingly similar to ours. In addition, Nelson *et al.*<sup>27</sup> recently demonstrated that dexmedetomidine converges on the natural sleep pathway to exert its sedative effects. Therefore, the similarity between the hypercapnic arousal phenomenon during dexmedetomidine infusions and natural sleep is not surprising. Previous studies during natural sleep, using special precautions to prevent the induction of arousal, have shown a consistent decrease in the HCVR response during different sleep stages (including slow-wave sleep).<sup>26,28</sup> Some factors that have the potential to cause arousal include sudden inhalation of carbon dioxide and changes in circuit odor, pressure, temperature, humidity, and resistance. Therefore, rebreathing methods (with no carbon dioxide in the initial bag mixture) have been used.<sup>26,28</sup> Belleville *et al.*,<sup>7</sup> using a pseudorebreathing technique





**Fig. 5.** Examples of different hypercapnic ventilatory responses during dexmedetomidine infusions. In *A* and *B*, arousal phenomena secondary to the hypercapnic stimulation are seen, and the Bispectral Index (BIS; dotted line) tightly correlates with the minute ventilation (MV; continuous line). *C* shows an absence of arousal where the BIS is not correlated with the MV.

(progressive computer-controlled increase in carbon dioxide), reported a modest decrease in the HCVR response after dexmedetomidine boluses, which is similar to what has been reported during natural sleep.<sup>26,28</sup> The HCVR discrepancy between the results of Belleville *et al.* and ours may lie in the fact that dexmedetomidine mimics natural sleep. By using the pseudorebreathing technique, Belleville *et al.* may have minimized the arousal phenomenon and thus observed a decreased HCVR re-



**Fig. 6.** Raw electroencephalographic tracing showing arousal from slow-wave sleep pattern during dexmedetomidine infusion. This tracing is plotted from the data of the arousal phenomenon shown on the middle panel of figure 7. The arrow labeled *Arousal* is positioned at the same time point as the similar arrow of the middle panel of figure 7.

sponse, as seen during natural sleep. On the other hand, our results have been contaminated by arousals caused by the sudden inhalation of carbon dioxide, which is a phenomenon previously described during natural sleep.

#### Respiratory Patterns

Dexmedetomidine and remifentanyl were associated with two very different patterns of ventilation. The opposite tendencies observed with  $Ti/Tt$  correlate well with other studies.<sup>9,29,30</sup>

**Table 4.** Summary of the Hypercapnic Ventilatory Response during Parts 1 and 2

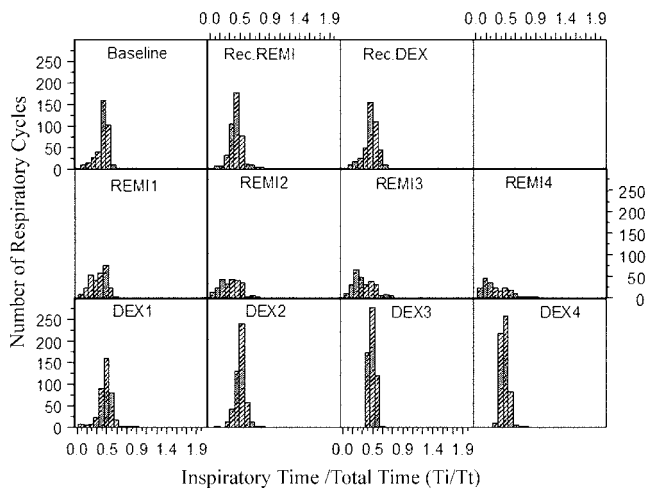
	$\Delta MV$	$\Delta CO_2$
Baseline	7.7 (4.0)	5.9 (2.9)
REMI1	2.8 (2.2)*	6.7 (4.7)
REMI2	3.6 (1.7)*	7.2 (4.0)
REMI3	4.3 (3.7)*	5.8 (3.)
REMI4	3.8 (2.4)*	7.7 (3.6)
Recovery	7.9 (2.0)	6.1 (2.6)
DEX1	8.2 (3.8)	4.9 (2.1)
DEX2	7.4 (4.0)	5.3 (2.7)
DEX3	6.4 (3.7)	4.4 (2.5)
DEX4	5.6 (3.6)	5.0 (4.0)

Values are presented as mean  $\pm$  SD.

\*  $P < 0.05$  from baseline.

$\Delta CO_2$  = arterial carbon dioxide tension ( $Paco_2$ ) at the end of the carbon dioxide challenge minus the  $Paco_2$  preceding the start of the carbon dioxide challenge;  $\Delta MV$  = minute ventilation at the end of the carbon dioxide challenge minus the minute ventilation preceding the start of the carbon dioxide challenge; DEX = dexmedetomidine; REMI = remifentanyl.





**Fig. 7.** Histogram of the timing component of the ventilation (Ti/Tt) for all steps. DEX = dexmedetomidine; Rec. = recovery from; REMI = remifentanyl.

### Histogram

Tidal volume/Ti and Ti/Tt values are usually summarized by their mean and SD.<sup>9,31-33</sup> However, drugs may have an effect on the shape of the distribution of these variables, as shown by our data (fig. 7). The distributions of baseline recovery from remifentanyl and from dexmedetomidine seemed to be similar, whereas the distributions of Ti/Tt during the four steps of remifentanyl were much flatter. Conversely, the four steps of dexmedetomidine seemed to have peaked.

A change in the shape of a distribution may result in a subtle change of mean and SD. For remifentanyl, while the mean value of Ti/Tt decreases, the SD has only a slight tendency to increase, which results in an increased coefficient of variation. Interestingly, Leino *et al.*<sup>9</sup> looked at the drug effect of morphine and oxycodone on the coefficient of variation of  $V_T$ ,  $RC/V_T$  (contribution of ribcage to  $V_T$ ), and RR. They found an increased coefficient of variation of RR during drug infusions of both morphine and oxycodone.

### Respiratory Rate and Apnea/Hypopnea Index

We observed a statistically significant increase in RR during dexmedetomidine, although Belleville *et al.*<sup>7</sup> reported a statistically significant decrease in RR. This discrepancy may result from the arousal phenomenon we reported and discussed earlier. This discrepancy could also result from the fact that boluses were used in the study of Belleville *et al.*, whereas we used infusions that resulted in sustained and higher dexmedetomidine concentrations. Interestingly, Ebert *et al.*<sup>6</sup> used dexmedetomidine infusions similar to ours, and that study showed a significant increase in RR as well.

The AHI analysis adds a clinical perspective. In the current investigation, obstructive apnea was observed during baseline, remifentanyl and dexmedetomidine infusions, and stages of deep sleep. However, the inci-

dence of these events was significantly higher with remifentanyl and significantly lower during dexmedetomidine infusions. At baseline, the number of subjects with an AHI greater than 15 is surprisingly high. Two factors may account for this finding. First, the prevalence of sleep-disordered breathing may be underestimated and is as high as 24% in healthy men.<sup>34</sup> Second, during this study, the subjects rested in a supine position and had a tight facemask attached, both of which may have exacerbated upper airway obstruction. Finally, the overall observed respiratory depression during remifentanyl infusions (table 2) is underestimated because two subjects who experienced prolonged apnea episodes leading to desaturations had to be prompted to breathe.

Central control of ventilation is complex and not yet well understood. Ample evidence suggests that  $\alpha_2$ -adrenergic activity plays a role in the modulation of respiratory control.<sup>35-37</sup>  $\alpha_2$  Receptors are located at multiple places in the central nervous system. The locus ceruleus, an important center for the sedative effect of these drugs,<sup>38</sup> has been shown to have a role in the control of ventilation and may serve as an alarm system. (Hypercapnia activates the locus ceruleus, which is associated with increase apprehension and which leads to the stimulation of the respiratory centers.<sup>5</sup>) Other central sites of action for  $\alpha_2$ -agonist drugs that have been implicated in breathing control include adrenergic cells of the rostral ventrolateral medulla,<sup>39</sup> the dorsal motor nucleus of the vagus,<sup>40</sup> neurons within the bulbar respiratory center,<sup>41</sup> and the nucleus ambiguus.<sup>37</sup> Peripheral tissues such as the carotid body or pulmonary vasculature have also been implicated in the respiratory effects of these drugs.<sup>42,43</sup>

Obstructive apnea has been reported after  $\alpha_2$ -agonist administration.<sup>7,44</sup> Obstructive apnea is produced by an imbalance between the dilating forces generated by upper airway muscles and the constricting luminal forces generated by the inspiratory thoracic muscles.<sup>45</sup> Recent evidence has shown vocal cord adduction and glottic closure secondary to recurrent laryngeal nerve activation during expiration by  $\alpha_2$ -adrenergic agonists in goats.<sup>37</sup> However, another recent study investigating the effect of clonidine in obstructive sleep apnea showed an overall improvement of the AHI during rapid eye movement sleep.<sup>4</sup>

Our methods had limitations. The number of subjects ( $n = 6$ ) included in the analysis is small. To overcome this limitation, the interindividual variability was minimized by limiting the study to young, healthy, nonobese men. Because of time constraints, the HCVR was measured at baseline and at only one level (5%) of carbon dioxide, as published by Peat *et al.*<sup>46</sup> The HCVR is not linear for the entire range of carbon dioxide. The lower end of the HCVR is flattened into a hockey stick-like shape, and the higher end (6% and greater) flattens off.<sup>17</sup>

Repetitive administration of carbon dioxide challenges

is another limitation of our method, because ventilation may be affected for several hours after a carbon dioxide challenge.<sup>17</sup> Finally, the pharmacokinetic profile of dexmedetomidine prevented us from randomizing the sequence of drug administered, and although it is controversial,<sup>47</sup> the possibility of acute opioid tolerance should be mentioned. In addition, the possibility that the increase in RR during dexmedetomidine infusions may be secondary to muscle exhaustion, and a consequence of the absence of randomization should be mentioned. However, this is unlikely because the RR is returning to baseline during recovery from dexmedetomidine.

## Conclusion

As expected, when compared with baseline, remifentanil infusions resulted in respiratory depression as evidenced by a decreased HCVR response, decreased RR and MV, respiratory acidosis, and increased AHI and apnea episodes resulting in desaturations. In addition, remifentanil substantially disturbed the natural pattern of breathing and flattened the distribution of Ti/Tt.

Dexmedetomidine did have some respiratory effects, as would be expected because (1) one of its sites of action is the locus ceruleus, which is known to play a role in both respiratory control and sleep modulation,<sup>5,38</sup> and (2) dexmedetomidine converges on the natural sleep pathway to exert its sedative effects,<sup>27</sup> whereas natural sleep does result in ventilation modulation.<sup>26,28,34,45,48,49</sup> However, the respiratory effects of dexmedetomidine were markedly different from those of remifentanil. Compared with baseline, during dexmedetomidine infusions, the HCVR response was unchanged, the RR was significantly increased, and the overall AHI was significantly decreased. The effect of dexmedetomidine on the breathing pattern also contrasts with the effect of remifentanil. The distribution of Ti/Tt showed an increased peak. More importantly, dexmedetomidine exhibited a hypercapnic arousal phenomenon similar to what has been described during natural sleep.

Clinically speaking, dexmedetomidine stands apart from other sedatives. Dexmedetomidine seemed clinically safe from a respiratory point of view, even during doses high enough to cause unresponsiveness to vigorous stimulation. Even supramaximal plasma concentrations of dexmedetomidine did not cause respiratory acidosis and did not cause prolonged apnea leading to desaturation, as was seen with relatively low plasma concentrations of remifentanil. Dexmedetomidine also exhibited a hypercarbic arousal phenomenon in a similar fashion to what has been described during natural sleep. The fact that dexmedetomidine mimics natural sleep could be seen to have significant positive clinical implications. Therefore, important clinical questions to be

addressed in future clinical studies on dexmedetomidine should include the following: (1) Could sedation with dexmedetomidine decrease the incidence of delirium in the intensive care unit?<sup>50</sup> (2) Could sedation with dexmedetomidine be restorative as natural sleep? (3) Could dexmedetomidine have an effect on the immune system as natural sleep has?

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