

# Ketamine Activates Breathing and Abolishes the Coupling between Loss of Consciousness and Upper Airway Dilator Muscle Dysfunction

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## ABSTRACT

**Background:** Procedural sedation is frequently performed in spontaneously breathing patients, but hypnotics and opioids decrease respiratory drive and place the upper airway at risk for collapse.

**Methods:** In a randomized, controlled, cross-over, pharmacologic study in 12 rats, we conducted acute experiments to compare breathing and genioglossus electromyogram activity at equianesthetic concentrations of ketamine, a noncompetitive N-methyl-D-aspartate receptor antagonist that combines potent analgesic with hypnotic action effects, *versus* propofol. In 10 chronically

### What We Already Know about This Topic

- Most hypnotics and sedatives predispose the upper airway to collapse by differential muscle suppression; upper airway muscles are more vulnerable than the diaphragm
- Limited experimental and clinical evidence suggest beneficial effects of ketamine on airway patency

### What This Article Tells Us That Is New

- In rats, ketamine anesthesia can stabilize breathing by increasing the genioglossus activity, duty cycle, and respiratory rate compared with sleep and propofol-induced unconsciousness

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instrumented rats resting in a plethysmograph, we measured these variables as well as electroencephalography during five conditions: quiet wakefulness, nonrapid-eye-movement sleep, rapid eye movement sleep, and low-dose (60 mg/kg intraperitoneally) and high-dose ketamine anesthesia (125 mg/kg intraperitoneally).

**Results:** Ketamine anesthesia was associated with markedly increased genioglossus activity (1.5 to fivefold higher values of genioglossus electromyogram) compared with sleep- and propofol-induced unconsciousness. Plethysmography revealed a respiratory stimulating effect: higher values of flow rate, respiratory rate, and duty-cycle (effective inspiratory time, 1.5-to-2-fold higher values). During wakefulness and normal sleep, the  $\delta$  ( $f = 6.51$ ,  $P = 0.04$ ) electroencephalogram power spectrum was an independent predictor of genioglossus activity, indicating an association between electroencephalographic determinants of consciousness and genioglossus activity. Following ketamine administration, electroencephalogram power spectrum and genioglossus electroencephalogram was dissociated ( $P = 0.9$  for the relationship between  $\delta/\theta$  power spectrum and genioglossus electromyogram).

**Conclusions:** Ketamine is a respiratory stimulant that abolishes the coupling between loss-of-consciousness and upper airway dilator muscle dysfunction in a wide dose-range. Ket-

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amine compared with propofol might help stabilize airway patency during sedation and anesthesia.

**H**YPNOTICS and opioids decrease respiratory drive and place the upper airway at risk for collapse. Opioids are respiratory depressants and induce a dose-dependent impairment of upper airway dilator muscle activity.<sup>1,2</sup> Hypnotics and sedatives,<sup>3–8</sup> including propofol,<sup>6,8</sup> isoflurane,<sup>7</sup> thiopentone,<sup>5</sup> and midazolam<sup>9,10</sup> predispose the upper airway to collapse, partly by decreasing upper airway muscle activity.<sup>3–6</sup> During transition from wakefulness to anesthetized states, all hypnotics and sedatives so far studied consistently impair upper airway integrity.<sup>5,11</sup> Despite transiently putting the airway at risk during transition, recent data suggest that certain anesthetics, including barbiturates<sup>11,12</sup> and isoflurane,<sup>13</sup> dose-dependently augment genioglossus activity with increasing depth of anesthesia.<sup>12,13</sup>

A pharmaceutical with sedative and analgesic activity, which also spares respiratory drive and airway patency, might solve these problems: Noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists such as dextromethorphan, nitrous oxide,<sup>14,15</sup> and ketamine are available. Ketamine combines potent analgesic with hypnotic actions, providing sedation and analgesia.<sup>16</sup> In critically ill children, a lower incidence of airway obstruction under ketamine compared with propofol sedation was observed.<sup>17</sup> The work of Drummond *et al.* on tongue muscle activity and airway obstruction during midazolam and ketamine sedation suggests beneficial effects of ketamine on airway patency.<sup>18</sup> Furthermore, ketamine is recommended in difficult airway situations where spontaneous respiration needs to be preserved in infants<sup>19</sup> as well as in adults.<sup>20</sup> Limited experimental evidence on the effect of ketamine on upper airway patency exists. A single well designed study compared the effects of halothane, thiopental, diazepam, and ketamine on hypoglossal and phrenic nerve activity in ventilated, vagotomized cats.<sup>21</sup> The investigators suggested that respiratory control of the tongue muscles and the diaphragm are in part mediated by different neural pathways and may also be associated with the anesthetic used. While an acute increase in anesthetic depth with halothane, thiopental, and diazepam differentially suppressed the activities of the hypoglossal and the phrenic nerves in a dose-dependent fashion, ketamine administration did not result in such a differential suppression, potentially translating to a better preservation of airway patency. Physiopharmacological data on the effects of ketamine on airway muscle function and ventilation in animals breathing spontaneously are needed as a first step to define in translational studies an optimal sedation regimen for distinct collectives of critically ill patients at risk for airway collapse.

In the preclinical work presented here we hypothesized that spontaneously breathing animals given ketamine would maintain breathing by one or both of two mechanisms: augmentation of airway dilator muscle activity and increased

inspiratory duty-cycle. Duty-cycle, also known as effective inspiratory timing, is defined as inspiratory time divided by total respiratory cycle time. Duty-cycle determines airway stability: an increase in duty-cycle can compensate for a partial airway obstruction.<sup>22</sup> Accordingly, we tested the hypothesis that genioglossus muscle activity is higher during ketamine anesthesia compared with both propofol anesthesia and rapid eye movement (REM) sleep. Our acute experiments compared propofol and ketamine given at equianesthetic doses. Results from these experiments, combined with previous observations of ketamine-induced tongue protrusions in rats,<sup>23</sup> encouraged us to test the additional hypotheses that ketamine sedation causes an increase in genioglossus activity and duty-cycle compared with wakefulness.

## Materials and Methods

We used 22 adult male Sprague-Dawley rats (300–400 g; Harlan Sprague-Dawley, Indianapolis, IN). All procedures involving animals were approved by the Institutional Animal Care and Use Committee at Beth Israel Deaconess Medical Center (IACUC, Boston, Massachusetts). Two sets of experiments were conducted, as depicted in figure 1.

### Protocol 1 (Acute Experiments): Comparison of Genioglossus Activity under Ketamine versus Propofol

In 12 rats, anesthesia was induced with 3% isoflurane, and maintained for surgical instrumentation with 1.5% isoflurane. We cannulated the femoral vein (for subsequent propofol administration), transected the trachea, and cannulated it with PE240 tubing, through which the rat spontaneously breathed. Rats lay in the supine position with the head supported in a neutral position in the midline on a soft piece of tissue. A temperature probe was inserted into the rectum and core temperature was regulated at  $37 \pm 1^\circ\text{C}$  using a heating pad. We then inserted by open surgery two insulated stainless steel wires (California Fine Wire Co., Grover Beach, CA) into the genioglossus muscle, one on each side of the midline. After surgery, we discontinued isoflurane and started an infusion of either ketamine (1,500  $\mu\text{g}/\text{kg}/\text{min}$ ) or propofol (500  $\mu\text{g}/\text{kg}/\text{min}$ ) in a crossover fashion, such that breathing and airway muscle function was studied in each subject under both anesthetics on the same study day (see fig. 1).

After 45 min of steady state infusion with ketamine or propofol, we performed intermittent tail-clamping maneuvers to determine the ED<sub>50</sub> as described by Orth *et al.* Briefly, tail clamping was applied and, depending on the response, the infusion was increased or decreased by 15%. This procedure was repeated every 10 min until two sequential responses just permitted and just prevented movement.<sup>24</sup> Measurements of pharyngeal pressure were made under zero-flow conditions at the transition point between inspiration and expiration. We measured breathing using pneumotachography for a period of 2 min at each measurement point. End-tidal carbon dioxide was measured by a CAPSTAR-100 Carbon Dioxide Analyzer (CWE Inc., Ardmore, PA).

Prot.	Intervention	Randomization	Measurement 1		Measurement 2		Measurement 3		
1	- Induction of anesthesia - GG EMG - Tracheostomy - iv and arterial line	Ketamine and propofol cross-over design	Individual titration ED <sub>50</sub>		45 minutes steady-state @ 0.66-fold and 1.5-fold ED <sub>50</sub> .	Second dose: 0.66-fold or 1.5-fold ED <sub>50</sub> (randomized)	45 minutes steady-state @ 0.66-fold and 1.5-fold ED <sub>50</sub> .	Third dose: 0.66-fold or 1.5-fold ED <sub>50</sub> (randomized)	
Prot.	Intervention	Randomization	Measurement 1		Measurement 2		Measurement 3	Measurement 4	
2	-Induction of anesthesia - GG and neck EMG - EEG - Seven days of recovery	Random order of measurements during wakefulness, sleep, and ketamine	Wakefulness	4 hours later	Sleep	1-4 days later	Ketamine (first dose: either 60 mg/kg or 125 mg/kg, randomized)	2-7 days later	Ketamine (first dose: either 60 mg/kg or 125 mg/kg, randomized)

**Fig. 1.** Protocols. Protocol 1: Acute experiments. In a randomized crossover study, rats were instrumented during isoflurane anesthesia. Subsequently, median effective dose values were calculated individually (Dixon's up and down method), and measurements of breathing, blood pressure, electrocardiogram, pharyngeal pressure, and genioglossus electromyogram were taken at three different effective doses of ketamine and propofol. Protocol 2: Experiments in chronically instrumented rats. After instrumentation with genioglossus muscle, neck muscle, and epidural electroencephalography electrodes, rats were allowed to recover for 7 days. Subsequently, measurements of breathing, electroencephalogram, and muscle activity were made in a plethysmography chamber during wakefulness, sleep, and ketamine anesthesia (two different doses). EEG = electroencephalogram; EMG = electromyogram; GG = genioglossus.

After measurements were taken at the ED<sub>50</sub> of ketamine or propofol, we applied the 0.66-fold ED<sub>50</sub> and the 1.5-fold ED<sub>50</sub> of the same anesthetic; the order was randomized and the second and third doses were administered for 45 min before measurements were taken. After respiratory measurements were finished at three different doses, we switched the anesthetic to complete the cross over study (fig. 1).

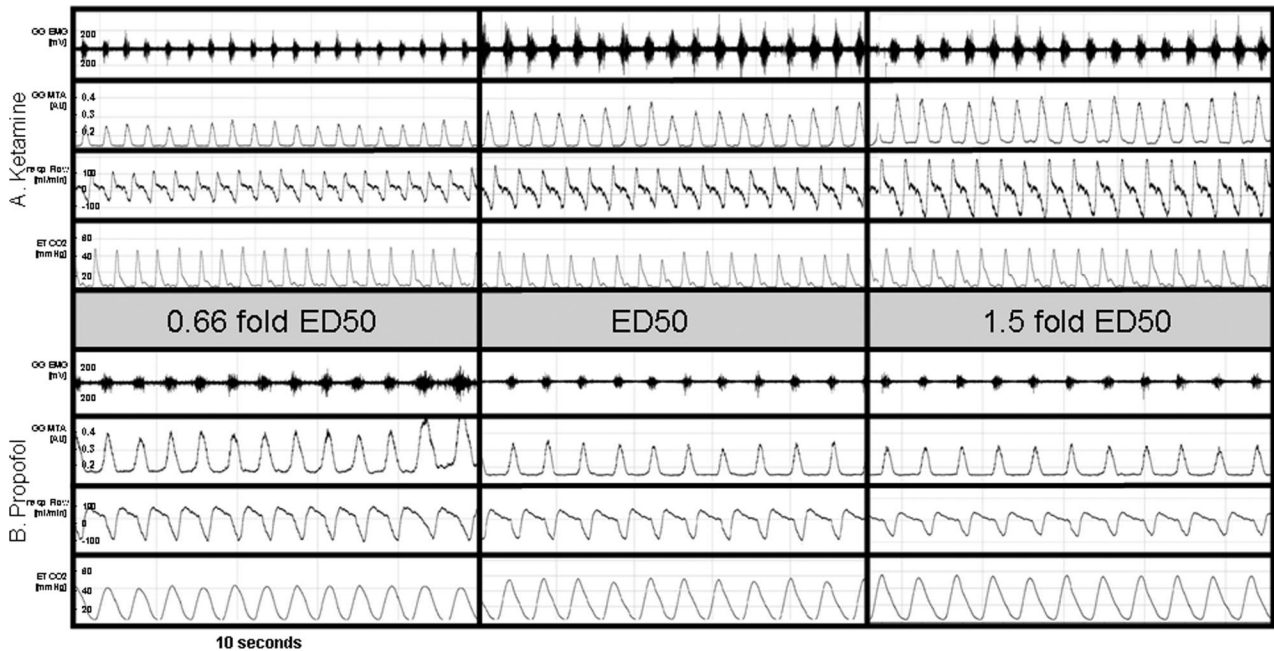
**Protocol 1 Analysis**

Genioglossus signals from acute experiments were amplified (Grass Polygraph, Grass Instruments, West Warwick, RI), band-pass filtered (100–1,000 Hz), and processed by a continuous moving time averager (CWE, Inc.; time constant 100 ms), analyzed with Clampfit (Molecular Devices, Sunnyvale, CA) and Igor Pro (WaveMetrics, Inc., Lake Oswego, OR). Analysis of these data were done by an investigator blinded to the anesthetic drug the rats had received. In anesthetized rats, genioglossus activity consistently varied with respect to the respiratory cycle (fig. 2). Tonic genioglossus activity was taken as the nadir genioglossus activity during expiration, minus genioglossus activity measured in the dead rat following euthanasia (reflecting the degree of electrical noise).<sup>25</sup> Phasic activity was defined as maximum in-

spiratory activity, minus tonic activity. Thus in acute experiments (protocol 1, see figs. 1 and 2) we compared phasic and tonic genioglossus activity under ketamine *versus* propofol.

**Protocol 2: Chronically Instrumented Rats, Comparison of Genioglossus Activity under Ketamine versus Wake and Sleep**

In order to compare the effects of ketamine on genioglossus activity with wakefulness and sleep, we chronically instrumented 10 rats with electrodes for genioglossus and neck electromyography, as well as cortical electroencephalogram.<sup>26</sup> Rats were anesthetized with chloral hydrate (350 mg/kg, intraperitoneally). Two flexible electromyography wire electrodes (Plastics One Inc., Roanoke, VA) were placed into the genioglossus muscle through a ventral incision. Another two electromyography wires were surgically implanted in the neck muscles, and all the wires were subcutaneously tunneled to the back of the head. For measurement of electroencephalogram-signals, two screw electrodes (Plastics One Inc.) were inserted into holes drilled into the skull, one approximately 1 mm anterior and one approximately 3 mm posterior to the bregma and approximately 1 mm lateral to the midline. The free ends of the leads were connected to a



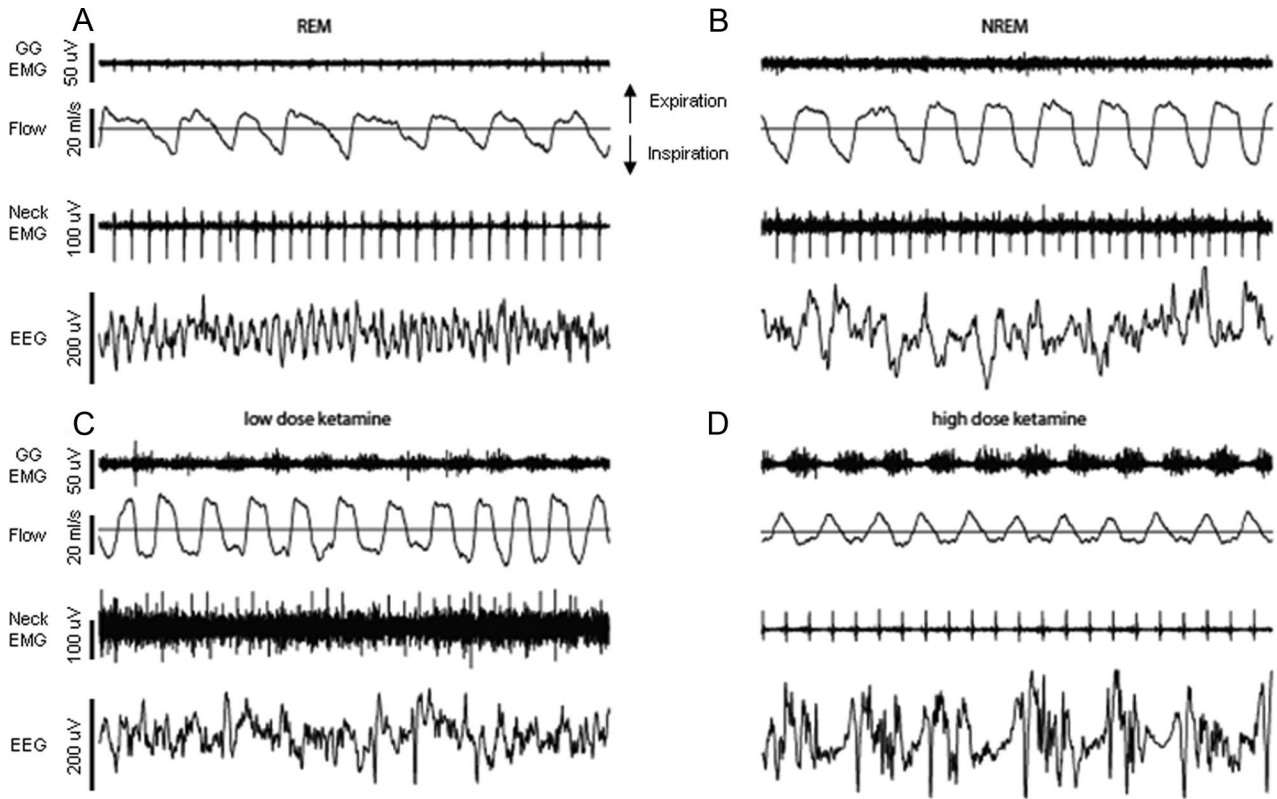
**Fig. 2.** Sample recordings from an acute experiment. (A) Ketamine anesthesia. Genioglossus electromyogram and respiratory flow increase with ketamine dose, whereas end-tidal carbon dioxide remains constant. (B) Propofol anesthesia. Genioglossus electromyogram and respiratory flow decrease with propofol dose, whereas end-tidal carbon dioxide increases. AU = arbitrary units; EMG = electromyogram; ET $\text{CO}_2$  = end tidal carbon dioxide; GG = genioglossus; MTA = moving time average; resp. flow = respiratory flow.

socket (Plastics One Inc.) that was then attached to the skull with dental cement. The incisions were closed with wound clips. Rats were allowed to recover at least 7 days. During each of three experimental days, rats were placed in a whole-body plethysmograph (Buxco Electronics, Sharon, CT) and measurements of breathing, muscle activity, and electroencephalogram were made after rats were given either placebo, low-dose (60 mg/kg intraperitoneally), and high-dose ketamine anesthesia (125 mg/kg intraperitoneally). Rats were then placed in the plethysmograph and the electroencephalogram/electromyogram recording cable was screwed to the connector on the rat's headset and connected to the recording equipment. Air leakage was prevented by sealing the hole through which the cable was placed in the plethysmograph with modeling clay. All rats received all three treatments in random order with at least 2 days between studies. All experiments were performed between 1:00 and 8:00 PM. After the third experimental day, rats were euthanized, the two wires inserted into the genioglossus muscle were stimulated electrically, and movements of the tongue were observed that verified the correct position of the wires.

### Protocol 2 Analysis

In awake, chronically instrumented rats (protocol 2), genioglossus activity, neck, and electroencephalogram signals were analyzed using Sleep Sign for Animals (Kissei Comtec Co., LTD., Nagano, Japan). Signals were amplified (Grass Polygraph, Grass Instruments), filtered (electromyography: 100–1,000 Hz; electroencephalogram: 0.5–100 Hz), digitized,

and stored on desktop computers for off-line analysis. The neck and genioglossus signals were digitally rectified and integrated. Although phasic genioglossus activity was always present under anesthesia, it was observed only intermittently in unanesthetized rats.<sup>27</sup> Since phasic genioglossus activity was not present consistently across wake and nonrapid eye movement (NREM) states, we were not able to quantitatively compare respiratory-related genioglossus activity under low-dose (60 mg/kg intraperitoneally) and high-dose (125 mg/kg intraperitoneally) ketamine anesthesia with that during wake and sleep. Instead, we measured average genioglossus activity without respect to the respiratory cycle during 10 s epochs during wake, sleep, and following ketamine administration. We measured genioglossus and neck muscle function as well as respiratory parameters at peak anesthetic effect 10–20 min after ketamine injection. On experimental days when ketamine was not administered, sleep stages were determined by analyzing the electroencephalogram and electromyogram signals as previously described.<sup>11</sup> Briefly, REM sleep was defined by two criteria:  $\theta/\delta$  ratio of greater than 1, and decrease in neck muscle activity (by 25% compared with NREM). Genioglossus activity during REM stage was very low (excluding bursts of twitches, see figs. 3 and 4). Episodes of tongue muscle twitches typically occurring during REM were not analyzed. NREM sleep was characterized by high  $\delta$ -activity (0.5 to 4 Hz) in the electroencephalogram, as well as closed eyes. Genioglossus activity was measured during episodes of REM and NREM sleep, and the averages for these two



**Fig. 3.** Representative recordings from a chronically instrumented rat. Measurements during sleep (A + B) and ketamine anesthesia (C + D). Genioglossus electromyogram was higher during ketamine anesthesia compared with sleep. During ketamine anesthesia, strong respiratory activity was present during wakefulness and sleep. The electroencephalogram during nonrapid eye movement sleep and ketamine anesthesia appears similar (predominantly slow-wave sleep), but different from rapid eye movement sleep (predominantly  $\theta$  waves). 5 s epoch. EEG = electroencephalogram; EMG = electromyogram; GG = genioglossus; NREM = nonrapid eye movement sleep; REM = rapid eye movement sleep.

stages were compared with values measured during quiet wakefulness (no movements, eyes open, neck muscle activity higher compared with sleep).

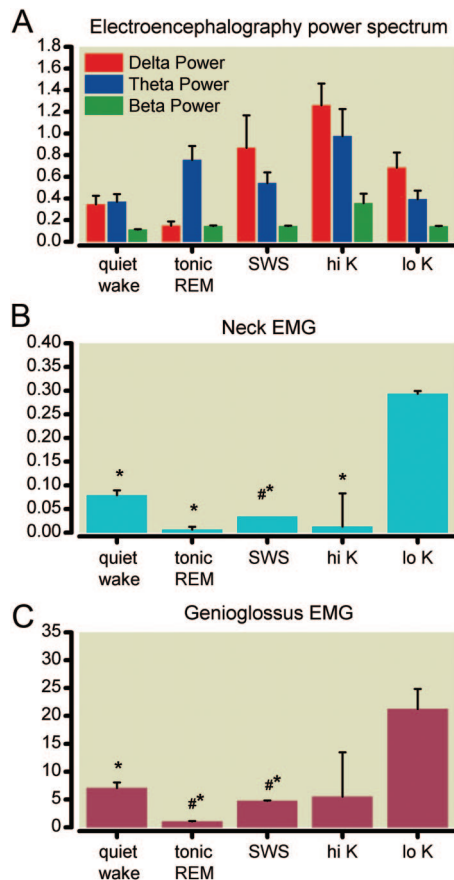
Respiratory variables were derived from the ventilatory flow signal (differential pressure between the plethysmograph experimental and reference chamber compensated for temperature and humidity and measured with a differential pressure transducer [Buxco Electronics]). The signal was analyzed with Biosystem XA software (Buxco Electronics) to obtain minute ventilation, tidal volume, respiratory rate, and inspiratory time. The raw signal was also rectified and integrated with Sleep Sign software (Nagano, Japan) to determine minute ventilation. The formula used to calculate minute ventilation and tidal volume is based on the work of Drorbaugh and Fenn<sup>28</sup>:  $\dot{V}_a(t) = \dot{V}_{\text{box}}(t) \frac{T_a P_{\text{box}}}{T_a P_{\text{box}} - T_{\text{box}} P_a}$ , where  $\dot{V}_a(t)$  is the estimated animal flow and  $\dot{V}_{\text{box}}(t)$  is the measured box flow (in and out of the chamber).  $T_a$  is the animal's body temperature,  $T_{\text{box}}$  is the chamber temperature,  $P_{\text{box}}$  is the dry pressure in the chamber, and  $P_a$  is the dry pressure within the animal. Beginning of inspiration is determined where the box flow signal passes about zero box flow in the inspiratory direction. Ending of inspiration is determined by the next beginning of inspira-

tion. A representative recording of genioglossus activity in a chronically instrumented rat is depicted in figure 3.

### Statistical Analysis

Sample size calculation for testing the primary hypothesis (genioglossus muscle activity is higher during ketamine anesthesia) in the rat studies was based on previously reported differences between the two anesthetics observed in the same rat model.<sup>13</sup> Accordingly, we expected that a sample size of 12 rats provides the appropriate power (0.8) to identify significant ( $P < 0.05$ ) differences in phasic and tonic genioglossus activity as well as duty-cycle between ketamine and propofol given at mean effective dose.

Using a hierarchical sequence, the four hypotheses (genioglossus activity as well as duty-cycle in protocol 1 and 2) were tested with an  $\alpha$ -error of 5% (two-tailed testing) without adjustment for multiple testing.<sup>29</sup> The following sequence was defined: first, we tested whether genioglossus electromyogram differs between states. Possible differences in duty-cycle were tested subsequently only if the hypothesis of no difference in genioglossus activity during ketamine anesthesia was rejected. With statistical comparison of both main criteria (genioglossus activity and duty-cycle) we first tested if variables differed in the acute experiments (protocol 1); sub-



**Fig. 4.** Chronically instrumented rats: Electroencephalography and electromyography measurements. (A) Electroencephalography power spectrum: Electroencephalogram during slow wave sleep and ketamine anesthesia look similar (high slow-wave frequency power), but different from wakefulness and rapid eye movement sleep. (B) Neck muscle electromyogram: Neck muscle electromyogram was significantly higher during low-dose, but not during high-dose ketamine anesthesia compared with (quiet) wakefulness and sleep. (C) Genioglossus electromyogram: Genioglossus electromyogram was significantly higher during ketamine anesthesia compared with wakefulness and sleep. \*  $P < 0.05$  versus low-dose ketamine anesthesia (60 mg/kg). #  $P < 0.05$  versus high-dose ketamine anesthesia (125 mg/kg). EMG = electromyogram; hi K = high-dose ketamine anesthesia; lo K = low-dose ketamine anesthesia; REM = rapid eye movement sleep; SWS = slow-wave sleep.

sequent tests were performed if, and only if, all previous tests were significant to compare variables in chronically instrumented rats. Statistical comparisons were made by using a mixed linear model (compound symmetry type). We used data from rats studied under protocol 1 and tested for an effect of the independent variables (fixed effects: “anesthetic agent” and “dose”) on the dependent variable phasic genioglossus activity and duty-cycle. In the acute experiments, we compared genioglossus activity and duty-cycle during six conditions: propofol 0.66-fold  $ED_{50}$ , propofol  $ED_{50}$ , propofol 1.5-fold  $ED_{50}$ , ketamine 0.66-fold  $ED_{50}$ , ketamine  $ED_{50}$ , and ketamine 1.5-fold  $ED_{50}$ . Subsequently, we used

data from all rats studied under protocol 2 and tested for an effect of the independent variables “stage” and “ketamine-dose” on average genioglossus activity (during 10 s epochs),<sup>27</sup> and duty-cycle. We compared average genioglossus activity during 5 “stages,” *i.e.*, wakefulness, NREM, REM sleep, low-dose, and high-dose ketamine anesthesia. Scheffé F test was used to correct and make multiple *post hoc* statistical comparisons. To examine the relationship between electroencephalogram waves ( $\delta$ ,  $\theta$ , and  $\beta$ ) and genioglossus electromyogram, a mixed model regression analysis was performed. The mixed regression model accounts for the nested sources of variability in the experiment: interindividual variability resulting from repeated measurements per subject and the between-subjects variability resulting from the relationship between electroencephalogram and genioglossus electromyogram. Parameters for the mixed regression model were computed using the xtreg command in STATA 10 (StataCorp 2007, College Station, TX). For testing the hypothesis that the correlation between electroencephalogram and electromyogram differs between the anesthetized and nonanesthetized state, Fisher’s z-transformation test was used to compare correlation coefficients (Pearson  $-\delta/\theta$ -power *vs.* genioglossus electromyogram) during ketamine anesthesia *versus* the nonanesthetized state. SPSS Version 11.0 (SPSS Inc., Chicago, IL) as well as SigmaStat Version 3.0 (SPSS Inc.) were used for the remaining portions of the statistical analysis.

## Results

A total of 22 rats (weight:  $383 \text{ g} \pm 21$ , [means  $\pm$  SD]) were included in this analysis.

### Protocol 1: Ketamine versus Propofol

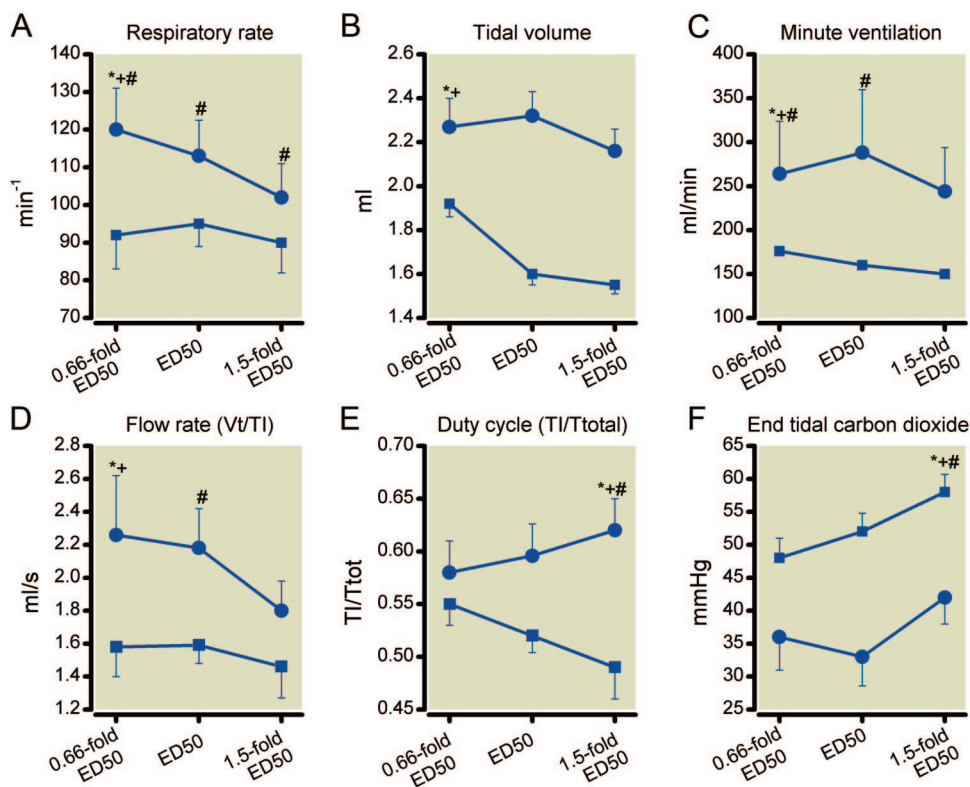
Data from 12 rats were included in the analysis of data derived from the acute experiments. The mean effective doses of ketamine and propofol were  $1.65 \pm 0.15$  and  $0.53 \pm 0.04$  mg/kg/min, respectively.

Ketamine compared with propofol anesthesia was associated with increased respiratory rate, tidal volume, flow-rate, and duty-cycle, resulting in lower values of end-tidal carbon dioxide (fig. 5). In addition, phasic and tonic genioglossus electromyogram were significantly greater during ketamine anesthesia (fig. 6). Of note, phasic (respiratory-related) genioglossus activity and duty-cycle (inspiratory time/total respiratory cycle time) were both dose-dependently increased during ketamine and decreased during propofol anesthesia (fig. 6).

### Protocol 2: Ketamine versus Behavioral State

10 chronically instrumented rats were included in the study. Two rats were excluded due to unstable recordings of genioglossus electromyogram. Eight rats were included in the data analysis.

The electroencephalographic spectra are shown in figure 4. Expectedly, based on the electroencephalogram-based def-



**Fig. 5.** Acute experiments: Breathing of tracheostomized rats during ketamine (circles) and propofol (squares) anesthesia. During ketamine anesthesia, breathing, represented by (A) respiratory rate, (B) tidal volume, (C) minute ventilation, and (D) flow rate, was augmented compared with propofol. Based on augmented breathing during ketamine anesthesia, (E) duty-cycle is increased, resulting in (F) lower end-tidal carbon dioxide values compared with propofol. \*  $P < 0.05$  for dose-effect (within anesthetic agent). +  $P < 0.05$  for an interaction effect (between anesthetic agents). #  $P < 0.05$  versus propofol, same effective dose (post hoc test). TI = inspiratory time; Ttot = total respiratory cycle time; Vt = tidal volume.

initions, electroencephalogram during REM sleep was characterized by high  $\theta$  power, whereas slow-wave-sleep was associated with high  $\delta$  power. The electroencephalogram spectra during ketamine anesthesia resembled those during slow-wave sleep, despite clear differences in the electroencephalogram waveforms (fig. 3).

Genioglossus activity was significantly higher during ketamine anesthesia compared with slow wave and REM sleep, both at 60 mg/kg and 125 mg/kg doses (fig. 4C). Nonrespiratory muscle (neck) activity was also increased compared with sleep and wakefulness after ketamine 60 mg/kg (fig. 4B).

Ketamine in chronically instrumented rats produced a dose-dependent increase in duty-cycle, a determinant of airway stability, compared with wakefulness and sleep. Ketamine 60 mg/kg was associated with an increased respiratory rate, tidal volume, minute ventilation, and flow-rate (fig. 7).

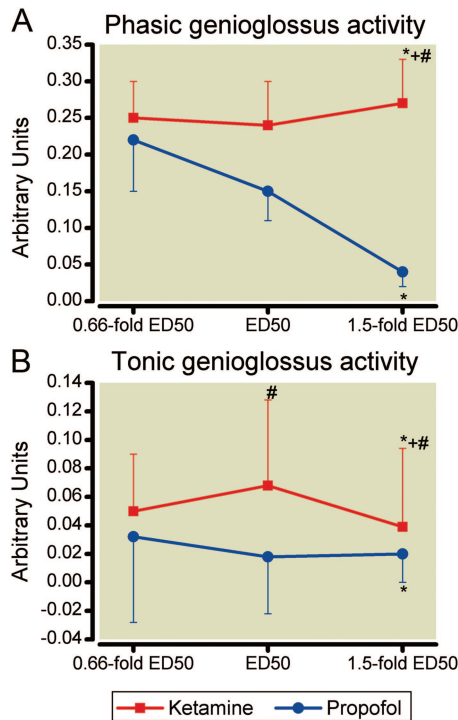
In the nonanesthetized state,  $\delta$  ( $f = 6.51$ ,  $P = 0.04$ ) electroencephalogram power spectrum was an independent predictor of genioglossus activity. In addition, there was a trend for  $\theta$  activity to predict genioglossus activity ( $f = -4.09$ ,  $P = 0.08$ ) (fig. 8). During ketamine anesthesia, electroencephalogram power spectra and genioglossus electromyogram were dissociated ( $P = 0.9$  and  $P = 0.5$  for relation

between  $\delta/\theta$  power spectra and genioglossus electromyogram, respectively). There was a statistically significant difference between the anesthetized and the nonanesthetized states in the association between electroencephalogram power and genioglossus electromyogram ( $\delta$ -power spectrum vs. genioglossus:  $P = 0.01$ ,  $\theta$ -power vs. genioglossus:  $P = 0.03$ , fig. 8).

## Discussion

We have shown that ketamine induced an increase in genioglossus electromyogram and duty-cycle compared with propofol anesthesia and sleep. Low-dose ketamine anesthesia stimulated breathing, resulting in higher values of flow-rate, respiratory rate, and duty-cycle. Compared with sleep and propofol anesthesia, ketamine induced loss-of-consciousness at the doses tested was accompanied by lower levels of upper airway dilator muscle dysfunction, represented by a potentiation of activity of the airway-stabilizing genioglossus muscle. Ventilation was preserved in a wide dose-range.

Ketamine's marked potentiation of the genioglossus electromyogram in accord with its dose-dependent increase in duty-cycle represent conditions that help stabilize upper airway patency. Phasic genioglossus activation increases air-



**Fig. 6.** Acute experiments: Phasic and tonic genioglossus activity during ketamine and propofol anesthesia. Genioglossus electromyogram was significantly higher during ketamine compared with propofol anesthesia. Phasic activity dose-dependently increased during ketamine and decreased during propofol anesthesia. (A) Phasic genioglossus activity dose-dependently increased during ketamine anesthesia and decreased during propofol anesthesia. (B) Tonic genioglossus activity increased during median effective dose of ketamine and decreased during high dose ketamine and propofol anesthesia. \*  $P < 0.05$  for dose-effect (within anesthetic agent). +  $P < 0.05$  for an interaction effect (between anesthetic agents). #  $P < 0.05$  versus propofol, same effective dose (*post hoc* test).

way-size<sup>30</sup> and decreases collapsibility.<sup>31</sup> Recent magnetic resonance imaging studies demonstrated that a neostigmine-evoked decrease in respiratory genioglossus activity in rats is associated with clear decreases in inspiratory upper airway volume<sup>25</sup> and thus presumably decreased upper airway resistance. Furthermore, ketamine induces a dose-dependent increase in duty-cycle. This mechanism can compensate for a partial airway obstruction.<sup>22</sup> Of note, in our study, the dose-dependent increase in duty-cycle was observed in animals breathing by the normal route as well as in tracheostomized animals, with the latter clearly having patent upper airways. Accordingly, we conclude that the increase in duty-cycle was not a compensatory mechanism for partial upper airway obstruction but rather represents a direct (beneficial) drug effect on inspiratory time.

Probably the most clinically interesting finding of this study was observed in our experiments in chronically instrumented rats: the dissociation of ketamine's opposing effects on the genioglossus (activation) and consciousness (inhibi-

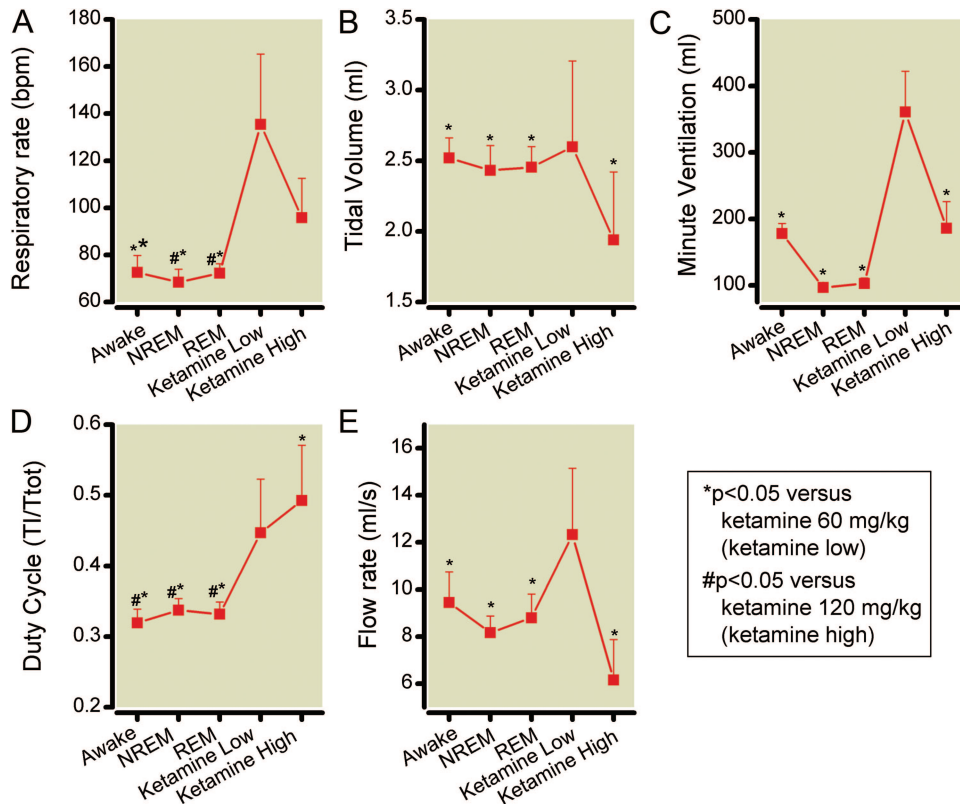
tion). The explanation for the uncoupling between loss-of-consciousness and upper airway dilator muscle dysfunction is unknown. However, it is most likely due to ketamine's atypical mechanism of action: blockade of NMDA receptors versus potentiation of  $\gamma$ -aminobutyric acid (GABA)ergic mechanisms. GABAergic anesthetics may compromise the airway by two mechanisms: muscle relaxation and respiratory drive suppression. Ketamine has neither of these effects. First, despite anesthesia and immobility, ketamine increased muscle tone at low anesthetic doses in the rat, and it did not decrease genioglossus electromyogram compared with wakefulness even at the highest dose applied (fig. 4). Second, ketamine anesthesia is associated with maintained activity in most of the forebrain arousal systems.<sup>32</sup> Thus, ketamine, unlike other anesthetics, preserves a high level of upper airway dilator muscle activity that is otherwise typically associated with consciousness.

Ketamine's cortical<sup>33,34</sup> and brainstem effects<sup>32</sup> differ from anesthetics such as isoflurane and propofol that potentiate GABA<sub>A</sub>ergic inhibition.<sup>32</sup> The molecular mechanism or mechanisms of ketamine's effects are not entirely clear. In contrast to GABA<sub>A</sub>ergic anesthetics, ketamine stimulates cholinergic, monoaminergic, and orexinergic arousal systems.<sup>32</sup> However, ketamine's anesthetic effects are thought to be mediated by NMDA antagonism.<sup>35</sup> NMDA receptor blockade appears to preferentially affect GABAergic versus glutamatergic cells, resulting in an excitatory effect at cortical and other forebrain sites.<sup>36</sup> Abnormal excitatory cortical activity can potentially impair consciousness in a manner similar to that which occurs during seizures, where spontaneous high amplitude synchronous discharges interfere with normal cortical function.<sup>37</sup>

The effects of ketamine observed in our study cannot be explained by direct effects at the pedunculopontine tegmental nucleus, where glutamine induces an increased genioglossus activity and a high variability of breathing.<sup>38</sup> Similarly, blockade of NMDA receptors in the hypoglossal motor nucleus would be expected to decrease respiratory genioglossus activity.<sup>39</sup> However, a potential disinhibitory effect on premotor neurons could explain ketamine's enhancement of muscle tone and function. Additional studies are requested to test this hypothesis.

Regarding respiratory timing, the duty-cycle change is probably related to the known effect of NMDA antagonists to increase inspiratory time.<sup>40</sup> In our acute experiments conducted in tracheostomized rats, flow-rate decreases while duty-cycle increases (fig. 5). In the chronically instrumented rats breathing *via* the anatomical route, both flow-rate and duty cycle are increased at low ketamine doses compared to propofol and sleep, but flow-rate was lower at high ketamine concentrations, whereas duty-cycle further increased (fig. 7). The combination of decreased flow rate (representing a decrease in respiratory drive), and increased duty-cycle may help stabilize upper airway patency during ketamine anesthesia. The latter is presumably due to increasing effects





**Fig. 7.** Chronically instrumented rats: Respiratory parameters following ketamine administration compared with those during spontaneous sleep and wake. Measurements were taken in a whole-body plethysmograph during wakefulness, sleep, and ketamine anesthesia: (A) respiratory rate, (B) tidal volumes, (C) minute ventilation, (D) duty-cycle, (E) flow rate. Ketamine-stimulated breathing: (A) respiratory rate, (E) flow-rate, and (D) duty-cycle were significantly higher during ketamine anesthesia compared with wakefulness and sleep. Rats were chronically instrumented and breathing by the normal anatomical route. \*  $P < 0.05$  versus low-dose ketamine anesthesia (60 mg/kg). #  $P < 0.05$  versus high-dose ketamine anesthesia (120 mg/kg). bpm = breaths/min; NREM = nonrapid eye movement sleep; REM = rapid eye movement sleep; TI = inspiratory time; Ttot = total respiratory cycle time.

of NMDA antagonists on inspiratory time, and the site of action is likely the rostral pons in or near the parabrachial complex.<sup>41</sup> This effect has been shown in nonhuman primates.<sup>42</sup>

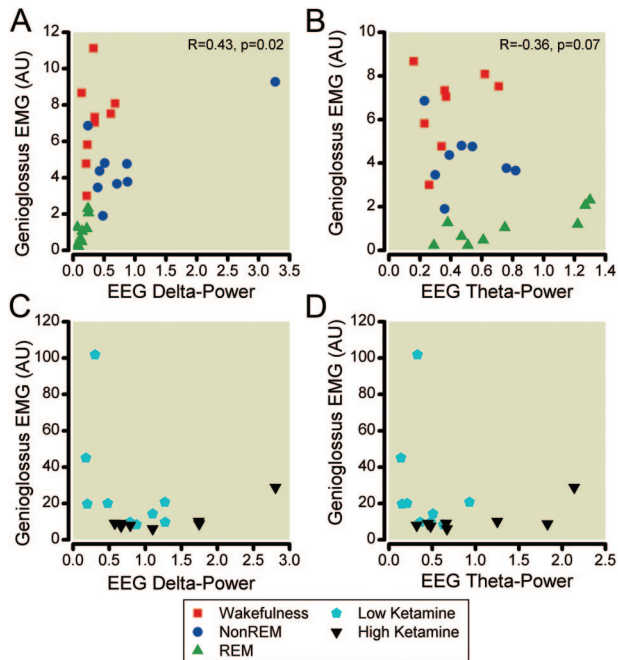
Like all anesthetics, ketamine at very high doses produces generalized, temporary brain dysfunction, including a global impairment of cortical and brainstem activity. Accordingly, at high doses, ketamine decreases the drive to the hypoglossal and phrenic nerves in cats<sup>21</sup> and decreases the respiratory rate.<sup>43</sup> Our study observed the highest genioglossus muscle activity levels at low (threshold anesthetic) doses of ketamine. However, even at more than twofold higher doses of ketamine, genioglossus activity, flow-rate, duty-cycle, respiratory rate, and tidal volume all were significantly higher compared with propofol at equianesthetic doses. Furthermore, genioglossus activity during high-dose ketamine and minute ventilation were not lower compared with wakefulness and sleep, and duty-cycle was significantly higher during ketamine compared with all conditions studied. Accordingly, ketamine's effects on upper airway dilator muscle activity and breathing studied in our rat model are most favorable

compared with GABAergic anesthetics (propofol and barbiturates), and also compared with sleep.

**Methodological Considerations**

The effects of anesthetics on respiratory muscles differ between species,<sup>44</sup> and it is unclear whether our findings translate to humans. Comparative studies in humans of the differential effects of various anesthetics on pharyngeal mechanics are clearly needed. Furthermore, we measured airway dilator muscle function and respiratory timing. To translate the observed findings to an increased airway stability, formal measurements of airway patency (upper airway closing pressure) are required. An increased upper airway closing pressure (to less negative values) has been demonstrated after neuromuscular blockade, partly due to an impaired response of the genioglossus muscle to negative pressure, and is associated with a less stable airway.<sup>45</sup>

In our crossover study all animals in protocol 1 received both ketamine and propofol in random order. Despite much shorter clinical effects, ketamine's plasma half-life in humans is 2 to 3 h after single injection and 79 min after continuous infusion, and two active metabolites are known.<sup>46,47</sup> Half-



**Fig. 8.** Chronically instrumented rats: Relation between electroencephalogram power spectrum and genioglossus electromyogram in chronically instrumented rats. Five repetitive measurements from eight rats. *Red symbols:* wakefulness; *blue symbols:* nonrapid eye movement sleep; *green symbols:* rapid eye movement sleep; *turquoise symbols:* low-dose ketamine anesthesia (60 mg/kg); *black symbols:* high-dose ketamine anesthesia (125 mg/kg). (A and B) Not anesthetized: genioglossus electromyogram positively correlates with  $\delta$  activity (A). There is a trend toward negative correlation with  $\theta$  activity (B). (C and D) During ketamine anesthesia: the relation between electroencephalogram and electromyogram is abolished, *i.e.*, sleep and genioglossus dysfunction are uncoupled. AU = arbitrary units; EEG = electroencephalogram; EMG = electromyogram; REM = rapid eye movement sleep.

life of propofol is 2–6 min after injection, but redistribution half-life is up to 60 min.<sup>47</sup> While we cannot exclude that active substances of the first anesthetic were active during measurements of the effects of the second, we are confident that this does not affect the conclusion of our randomized controlled crossover study.

Different study conditions between the acute and chronic protocols might account for the differences in genioglossus electromyogram and flow rate between both protocols. While we cannot pinpoint the mechanisms leading to these differences, possible mechanisms include: differences in carbon dioxide levels, duration of anesthesia, or pharyngeal pressure resulting from tracheostomized *versus* nontracheotomized conditions, varying amounts of airway secretions resulting from different durations of ketamine exposure, as well as carryover effects from previously administered anesthetics.

### Possible Clinical Implication

Ketamine is a safe and valuable alternative to etomidate for tracheal intubation in critically ill patients.<sup>48</sup> Ket-

amine or other more selective NMDA receptor antagonists<sup>14,15</sup> may represent an alternative to GABAergic drugs like propofol when deep sedation or light analgesia are required in the intensive care unit or for procedural sedation in patients with upper airway vulnerability. Upper airway dilator muscle activity is critically important in patients presenting with increased extraluminal pressure or partial intraluminal obstructions. Examples resulting in this condition include, but are not limited to, subcutaneous neck hematoma impairing spontaneous ventilation, an increased amount of fat tissue in obese patients, or patients with increased airway secretions further minimizing the airway size in the vulnerable perioperative period. NMDA receptor antagonists might be beneficial in such a scenario. Despite increasing genioglossus muscle activity and duty-cycle, which may have clinically important effects on pharyngeal mechanics, ketamine anesthesia can also put the airway at risk when high doses are administered. Differences between individuals in drug metabolism systems and responses to ketamine make it challenging to define “safe” ketamine doses. To reduce the likelihood of adverse outcomes, it is not safe to administer ketamine or any other anesthetic to patients with difficult airways, without having appropriate equipment and knowledgeable, skilled staff available.<sup>49</sup> Many questions need to be addressed before its use can be seriously considered for treatment of sleep disordered breathing. Ketamine is a controlled substance and has been abused.<sup>50</sup> It has hallucinogenic effects, and some have recommended that ketamine should be contraindicated in patients with known or suspected schizophrenia.<sup>51,52</sup> Another concern is that despite providing a favorable hemodynamic profile in specific intensive care unit populations<sup>53</sup> and maintaining sympathetic activity in response to hypotension, ketamine may increase arterial blood pressure by augmenting efferent sympathetic outflow.<sup>54</sup> Therefore, ketamine sedation and analgesia may not be used in case of current myocardial ischemia or severe arrhythmias.

In summary, ketamine sedation and light analgesia in rats is associated with markedly increased genioglossus electromyogram compared with propofol and sleep, and is associated with higher values of flow-rate, respiratory rate, and duty-cycle. Ketamine is a respiratory stimulating hypnotic and analgesic that abolishes the coupling between loss-of-consciousness and upper airway dilator muscle dysfunction.

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