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Susceptibility to Upper Airway Obstruction during Partial Neuromuscular Block

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Background: Airway obstruction after anesthesia may be caused or exaggerated by residual neuromuscular block, with loss of muscle support for collapsible upper airway structures.

Methods: Six male volunteers were studied before treatment, during stable partial neuromuscular block with vecuronium at a mean train-of-four (TOF) ratio of 50% (95% CI, 36–61%), and after reversal by neostigmine. Catheter-mounted transducers were placed in the pharynx and esophagus to estimate, respectively, the upper airway resistance, and the work of breathing (calculated as the time integral of the inspiratory pressure developed by the respiratory muscles, esophageal pressure time product) during quiet breathing, during breathing 5% carbon dioxide, and while breathing with an inspiratory resistor. Breathing with pressure at the airway opening held at pressures from –5 to –40 cm H₂O were also tested to assess airway collapsibility.

Results: Although breathing through a resistor increased upper airway resistance from 1.2 (0.67, 1.72) cm H₂O · l⁻¹ · s to 2.5 (1.32, 3.38) cm H₂O · l⁻¹ · s, and carbon dioxide stimulation reduced resistance to 0.8 (0.46, 1.33) cm H₂O · l⁻¹ · s, no effect of partial neuromuscular block (mean TOF ratio, 52%) on upper airway properties could be shown.

Conclusions: Neuromuscular block with a TOF ratio of 50% can be present yet clinically difficult to detect in patients re-

covering from anesthesia. This degree of block has no effect on airway patency in volunteers, even during challenge. Airway obstruction during recovery from anesthesia thus is more likely to be caused by residual effects of general anesthetic agents or centrally acting analgesics, either alone or perhaps in concert with residual neuromuscular block. (Key words: Airway collapse; airway resistance; inspiratory effort; muscles; respiratory.)

PARTIAL neuromuscular block can impair swallowing and airway control even if patients have sufficient respiratory muscle strength to maintain normal ventilation.^{1,2} The residual action of neuromuscular blocking agents thus may play a part in respiratory obstruction in patients recovering from anesthesia, although the importance of this factor is often difficult to separate from other causes.^{3,4} Upper airway obstruction is a frequent cause of hypoxic events during recovery from anesthesia, often caused by suppression of reflexes that act to maintain patency of the upper airway, by sleep, or by centrally acting agents such as residual anesthetics and postoperative analgesics.⁵

Residual neuromuscular block can be difficult to detect clinically⁶ and is often present in patients recovering from surgery.^{7,8} To simulate the presence of residual neuromuscular blocking effects and assess the potential contribution of this single factor to airway obstruction, without other factors such as sedation, analgesia, or sleep, we studied volunteers with a stable degree of partial neuromuscular block. We tested the hypothesis that (1) a moderate degree of neuromuscular block would increase airway resistance and respiratory effort, under conditions of resting breathing, or (2) that an increase in resistance might become apparent during stimulated breathing or when airway collapse was encouraged by an inspiratory resistance. We also directly tested the ability of the upper airway to resist collapse when subjected to exaggerated subatmospheric pressure. Each of these latter maneuvers reduces pharyngeal pressure during inspiration so that the airway will narrow if the counteracting dilator muscles are not strong

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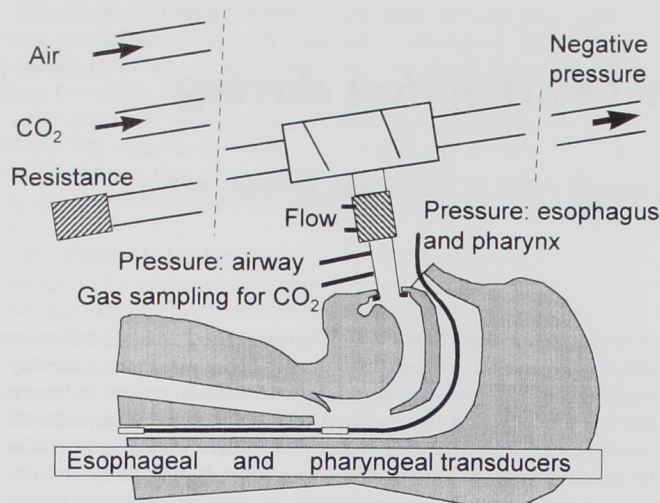


Fig. 1. Experimental layout showing the esophageal catheter with two transducers. The pressure difference between the mouthpiece and pharynx was used to calculate upper airway resistance.

enough. Any decrease in caliber further increases the airway resistance, thus limiting the flow through a critically narrowed segment.

Materials and Methods

After we received approval from the local ethic committee and informed consent, we studied six healthy men (aged 40 ± 6 yr; weight, 71 ± 5 kg; height, 174 ± 9 cm; values are expressed as means \pm SD). A catheter with two transducers mounted in it (Gaeltec, Dunvegan, Isle of Skye) was inserted (using local anesthetic gel in the nostril) so that the distal transducer lay in the esophagus and the proximal transducer was in the lower pharynx, between the posterior tongue and the tip of the epiglottis. The position of the proximal transducer was confirmed by a lateral radiograph of the neck. The esophageal transducer position was confirmed by minimal change in the difference between airway and esophageal pressure during attempted inspiration with the airway occluded. Each volunteer then lay supine in a comfortable position, wore a noseclip, and breathed *via* a flanged mouthpiece from a one-way valve system. A resistance ($10 \text{ cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$) or a large balloon containing 5% carbon dioxide, 21% oxygen, balance nitrogen could be connected to the inspiratory limb. Figure 1 illustrates the experimental layout.

Flow was measured at the mouthpiece with a pneu-

motachograph (Fleisch 2) and a differential pressure transducer (Validyne MP45, Northridge, CA), and then was integrated to give volume. Respiratory rate and minute volume were calculated from these signals. Pressure at the mouthpiece was measured using a transducer (Validyne MP45). Gas was sampled at the mouthpiece and analyzed for carbon dioxide (F_{CO_2} ; Datex Normocap 200, Instrumentarium Corp., Helsinki, Finland). A measure of the ventilatory response to carbon dioxide was calculated for each volunteer from the changes in ventilation and end-tidal carbon dioxide breathing periods. The signals were digitized at 128 Hz and recorded on a computer using a commercial acquisition system (MP100, Biopac, Goleta, CA). Upper airway resistance was calculated from the pressure difference between the mouthpiece and the supraglottic transducer (DP_{uaw}) obtained at an inspiratory airflow of 0.3 l/s. To exclude the possibility that airway collapse might occur at greater inspiratory flows, when the airway pressure is more greatly reduced, we also measured the flow resistance between flow values of 50–100% of the maximum inspiratory flow of each volunteer. To detect flow limitation, we inspected the plots of DP_{uaw} *versus* flow for each measurement period, to determine if flow remained unchanged despite a decrease in pharyngeal pressure. Finally, we also examined the flow *versus* time profile for flattening, which indicates inspiratory flow limitation⁹; that is, a constant flow over a range of pharyngeal pressure gradients.

An estimate of resistance of the glottis and lung was calculated using the method of Mead and Whittenberger¹⁰:

$$R_{\text{glottis+lung}} = [(P_{\text{es}} - P_{\text{ph}}) - (V/C_{1 \text{ dyn}})]/\dot{V}$$

where V is the instantaneous volume of the breath obtained by integration of the air flow, $C_{1 \text{ dyn}}$ is the dynamic compliance of the lung for that breath, \dot{V} is the airflow, and P_{es} and P_{ph} are the pressures in the esophagus and pharynx, respectively. $C_{1 \text{ dyn}}$ is calculated from the difference of the values of P_{es} when flow is zero at the start and end of inspiration, and the integrated tidal volume. The mean value of $R_{\text{glottis+lung}}$ over the entire inspiratory cycle was calculated. For each participant, the mean value of 20 successive breaths over the last 2 min of each measurement period was calculated, after exclusion of breaths for which artifacts such as swallowing had distorted the signals.

The esophageal pressure/time product was calculated as the area enclosed by esophageal pressure and the predicted chest wall recoil pressure¹¹ over the duration of

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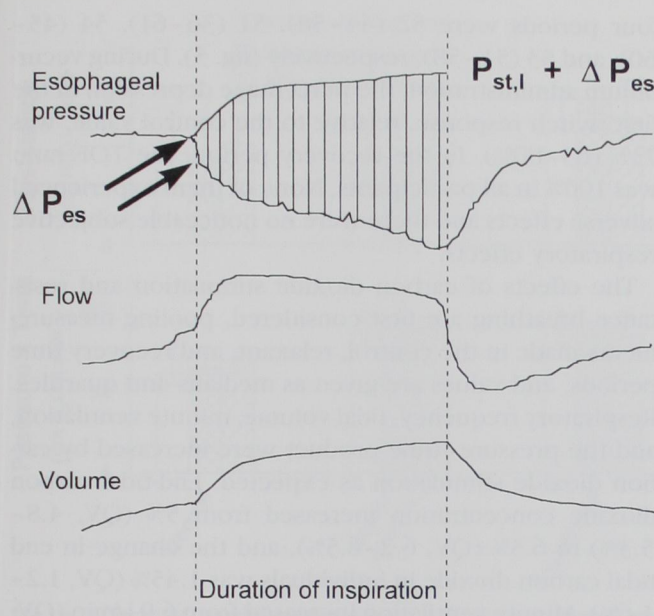


Fig. 2. Estimation of the esophageal pressure-time product. The static recoil pressure of the chest wall ($P_{st,l}$) is predicted from the change in lung volume and the esophageal pressure difference associated with incomplete lung emptying (ΔP_{es}) added to this. ΔP_{es} is measured from the change in P_{es} at the onset of inspiration. The pressure difference (indicated by the vertical distances) between the predicted value of the chest wall pressure and the esophageal pressure is the pressure produced by the respiratory muscles to generate inspiration. The integral of this pressure with respect to time during inspiration is taken as the pressure-time product per breath.

inspiration (fig. 2). This value was multiplied by respiratory frequency to give values measured in $\text{cm H}_2\text{O} \cdot \text{s} \cdot \text{min}^{-1}$. This measurement provides an index of respiratory work,¹²⁻¹⁴ which would increase if respiratory resistance were augmented.

Volunteers were studied in three time periods, each lasting approximately 24 min: first, a control period (CONTROL), second a period in which a stable partial neuromuscular block was obtained by vecuronium (NMB), and finally a period after the block had been antagonized by neostigmine (RECOV). Within each time period, measurements were made under four conditions: breathing normally (normal), breathing 5% carbon dioxide (CO_2), breathing with an inspiratory resistance (Res), and breathing against a negative pressure (collapse). For the first three breathing conditions, the participants were allowed to become accustomed to breathing in that way for 6 min and then measurements were made in the last 2 min. Figure 3 shows typical traces from a single participant. The last measurement

condition was intended to assess the negative pressure required to cause airway collapse. The pressure at the mouthpiece was reduced progressively in steps of 5 $\text{cm H}_2\text{O}$ every three respiratory cycles, until airway pressure was reduced to $-40 \text{ cm H}_2\text{O}$. This was done by connecting the inspiratory limb of the breathing system to a resistance of $2 \text{ cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ and the expiratory limb to an adjustable high-flow vacuum. The pressure at the mouthpiece could be held at the desired value by adjusting the flow. If airway collapse did not occur, evidence of flow limitation was sought. We inspected the pressure-flow plot of each participant for features of either constant or decreasing flow rate despite an increase in the difference between the mouthpiece and supraglottic pressure¹⁵ (fig. 4).

A venous cannula was placed in the dominant forearm and connected to a slow infusion of 0.9% sodium chloride. After careful skin preparation, Myotest skin electrodes were placed over the ulnar nerve at the wrist in the other arm, and supramaximal stimuli were applied (four stimuli in 2 s, repeated every 10 s) using a Myotest stimulator (Biometer, Odense, Denmark). The resultant contractions of the adductor pollicis were measured with a force transducer and recorder (Myograph 200, Biometer). After the control period measurements, a bolus dose of 1 mg vecuronium was given intravenously and the effects were noted. A further smaller bolus dose was given if necessary and then an infusion of

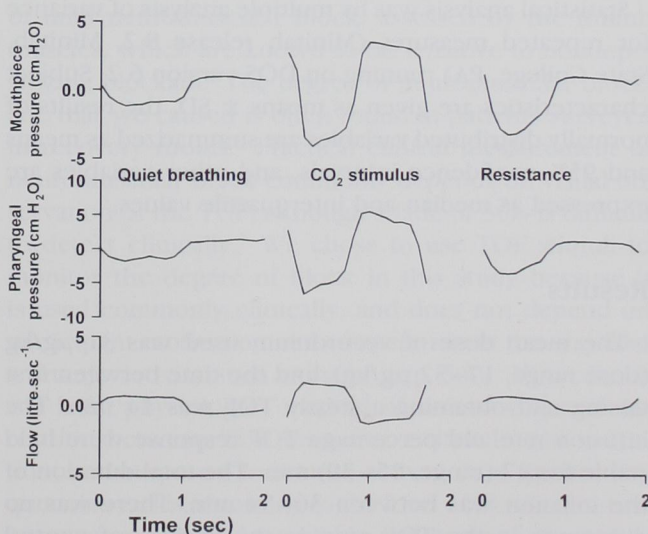


Fig. 3. Typical traces of mouth and pharyngeal pressures, and airway flow, during breathing in the control state, during breathing 5% carbon dioxide, and breathing through an inspiratory resistance.

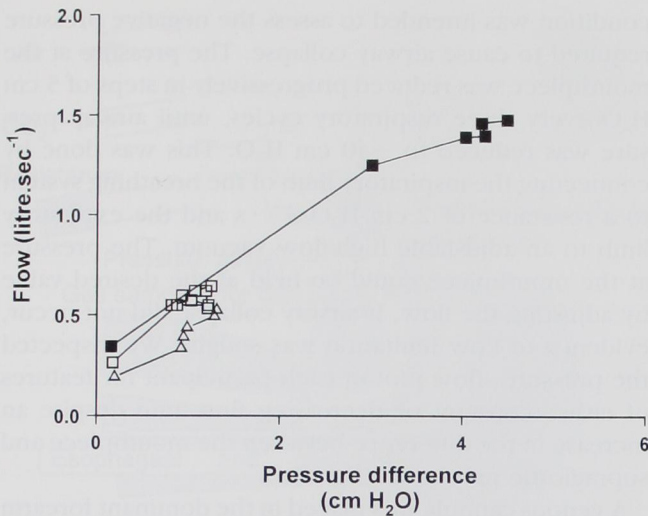


Fig. 4. Typical plot of inspiratory flow versus the pressure difference between the mouthpiece and pharynx. Open squares: normal breathing. Filled squares: during carbon dioxide breathing; open triangles: with inspiratory resistance.

approximately $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was started and the rate adjusted to maintain the train-of-four (TOF) ratio close to 50%.

Measurements were not started until the infusion rate and the response had been constant for at least 10 min. After the relaxant period measurements, the infusion was discontinued and each participant was given 2 mg neostigmine and 1 mg atropine intravenously.

Statistical analysis was by multiple analysis of variance for repeated measures (Minitab release 8.2, Minitab, State College, PA) running on DOS version 6.2. Subject characteristics are given as means \pm SD, the results of normally distributed variables are summarized as means and 95% confidence intervals, and other variables are expressed as median and interquartile values.

Results

The mean dose of vecuronium used was $31 \mu\text{g}/\text{kg}$ (dose range, 17–52 $\mu\text{g}/\text{kg}$), and the time between first dosing and obtaining a steady TOF was 14 min. The infusion rate and percentage TOF response were held stable for 27 (range, 15–39) min. The total duration of the infusion was between 36–54 min. There was no difference in the TOF ratio in the periods of control breathing, breathing with the carbon dioxide stimulus, breathing against the resistance, and breathing with the negative pressure. The percentage TOF values for these

four periods were 52 (44–58), 51 (36–61), 54 (45–60), and 53 (51–58), respectively (fig. 5). During vecuronium administration, the percentage depression of the first twitch response, relative to the control value, was 73% (63–80%). In the recovery period, the TOF ratio was 100% in all participants. None of them experienced adverse effects and there were no noticeable subjective respiratory effects.

The effects of carbon dioxide stimulation and resistance breathing are first considered, pooling measurements made in the control, relaxant, and recovery time periods, and values are given as medians and quartiles. Respiratory frequency, tidal volume, minute ventilation, and the pressure-time product were increased by carbon dioxide stimulation as expected. End-tidal carbon dioxide concentration increased from 5% (QV, 4.8–5.3%) to 6.5% (QV, 6.2–6.5%), and the change in end tidal carbon dioxide in individuals was 1.45% (QV, 1.2–1.6%). Minute ventilation increased from 6.9 l/min (QV, 6.5–7.7 l/min) to 16.6 l/min (QV, 14–18.7 l/min). These changes were accompanied by a reduction in airway resistance, from 1.2 (QV, 0.67–1.72) $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ to 0.8 (QV, 0.46–1.33) $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$. As expected, the pressure-time product increased, from 117 (QV, 83–138) $\text{cm H}_2\text{O} \cdot \text{s} \cdot \text{min}^{-1}$ to 275 (QV, 223–442) $\text{cm H}_2\text{O} \cdot \text{s} \cdot \text{min}^{-1}$. The presence of the inspiratory resistance did not alter frequency, tidal volume, or ventilation, but the pressure-time product increased to 255 (QV, 219–419) $\text{cm H}_2\text{O} \cdot \text{s} \cdot \text{min}^{-1}$ and airway resistance increased to 2.5 (QV, 1.32–3.38) $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$. The

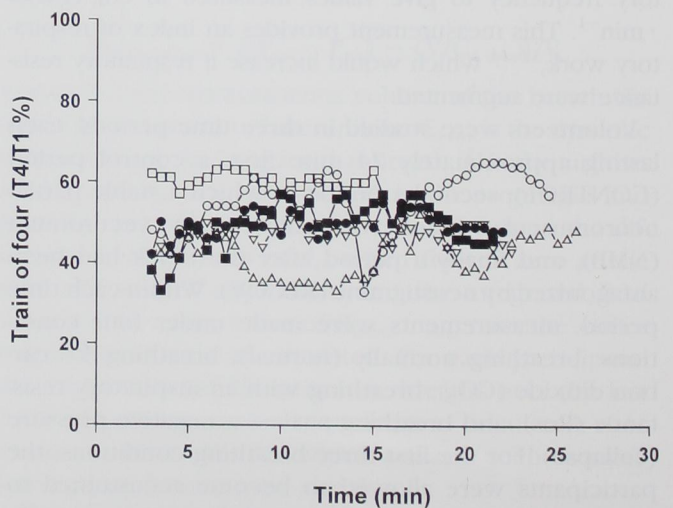


Fig. 5. Train-of-four ratios for each volunteer during the measurement period, to indicate the range and stability of the neuromuscular block.

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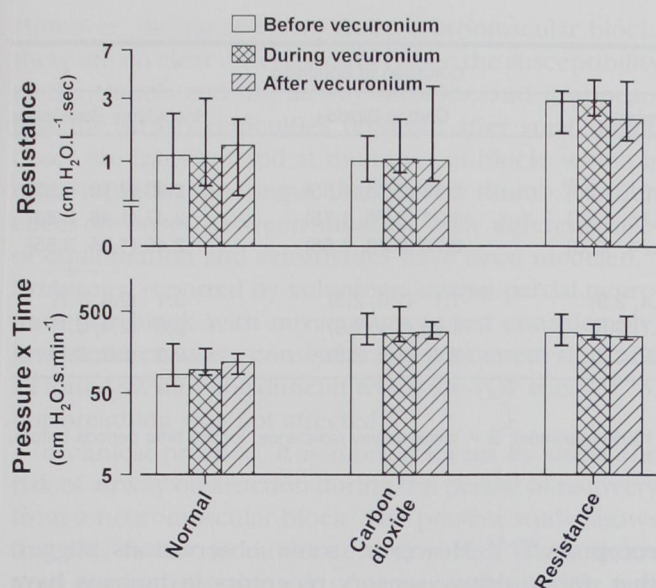


Fig. 6. Effects of partial neuromuscular block (relaxant) on upper airway resistance and the pressure-time product, during normal breathing, breathing carbon dioxide, and breathing through a resistor. Values are medians and 95% confidence intervals. There were no significant changes in either variable with neuromuscular block or antagonization of the block.

changes in resistance and pressure-time product with state were significant ($P = 0.013$ and $P < 0.001$, respectively).

Considering changes in variables associated with the presence of partial neuromuscular block and after reversal of this block, ventilation during air breathing and during carbon dioxide breathing were not affected. In addition, the response to carbon dioxide was not affected. The carbon dioxide response slopes were 7.8 (QV, 5.5-8.7) l/%CO₂ during air breathing, 5.9 (QV, 3.2-8.3) l/%CO₂ during vecuronium administration, and 7.8 (QV, 5.8-10.3) l/%CO₂ after antagonizing the effects of vecuronium. These changes were not significant. There were no significant changes in either airway resistance or pressure-time product when partial neuromuscular block was produced or antagonized ($P = 0.336$ and 0.993 , respectively; fig. 6). Considering breathing with the inspiratory resistor, when changes should have been most pronounced, airway resistance changed from 2.93 (QV, 1.53-4.41) cm H₂O · l⁻¹ · s to 2.64 (QV, 1.32-3.29) cm H₂O · l⁻¹ · s and pressure-time product from 272 cm H₂O · s · min⁻¹ (QV, 191-457) to 256 (QV, 225-350) cm H₂O · s · min⁻¹, respectively (fig. 6). No significant changes were noted in the resistance measured at greater flow rates, between 50-100% maxi-

mum (table 1). The median maximum flow rate in the control state was 0.65 l/s, and during neuromuscular block this changed to 0.53 l/s. This table also shows the values for lower airway resistance. There were no significant changes between any time period.

When the pressure at the airway opening was progressively decreased to -40 cm H₂O, no participant showed evidence of airway collapse or flow limitation, at any time period.

We did not have prior information on airway resistance changes to allow estimation of sample size. To exclude the possibility of a type 2 error, we conducted a retrospective power analysis of the study, using the standard deviation of the changes in resistance that were found with partial neuromuscular block.¹⁶ We considered that the changes in airway resistance reported after midazolam administration would be clinically relevant,¹⁷ and that a power of 0.8 was adequate. The values gave a ratio of relevant change:SD of change (the standardized difference¹⁶) that was greater than 3.37, and therefore the power of the study was sufficient to demonstrate clinically relevant changes in airway resistance. For the changes during unstimulated breathing, the power of the study was approximately 0.9.

Discussion

In this study, we tried to maintain a constant degree of mild neuromuscular block, assessed by the thumb muscles, which are known to be sensitive to nondepolarizing blockade. The degree of neuromuscular blockade that we caused is often found in patients surveyed in recovery rooms.⁶ Practical clinical measurement of neuromuscular block commonly depends on visual observation of the TOF, although a fade of 50% is difficult to detect clinically.⁶ We chose to use TOF stimuli to monitor the degree of block in this study because it is used commonly clinically, and does not depend on participant motivation and cooperation in the way that a tetanic activity such as hand grip does. However, it is a less "physiologic" method of assessment, and the relation between TOF response, twitch height reduction, and response to tetanic activation at greater frequencies varies according to the level of block, the state of onset or offset of the block, and perhaps the agent. We estimate that the level of paralysis with vecuronium in our volunteers would be equivalent, during recovery, to more than 10% depression of hand muscle force

Table 1. Changes in Airway Resistance

	Condition of Breathing		
	Normal	Carbon Dioxide	Inspiratory Resistance
A: Upper airway resistance (50–100% maximum flow)			
Control	1.03 (0.61, 1.36)	1.16 (0.74, 1.55)	2.83 (2.16, 4.37)
Neuromuscular block	1.27 (0.76, 1.61)	1.21 (0.76, 1.78)	2.47 (1.46, 3.88)
Recovery	1.40 (0.74, 1.30)	0.73 (0.48, 1.56)	2.49 (1.65, 3.85)
B: Lower airway resistance			
Control	2.3 (1.4, 2.9)	1.1 (1.0, 2.3)	3.1 (2.4, 3.7)
Neuromuscular block	2.4 (1.7, 2.6)	1.95 (1.4, 2.5)	2.6 (2.4, 3.1)
Recovery	1.4 (1.2, 2.3)	2.3 (1.5, 2.8)	2.3 (2.2, 2.7)

Values are median and quartiles ($\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$).

A = upper airway resistance measured when flow rates were between 50% and 100% maximum; B = lower airway resistance, for the time periods before, during, and after antagonization of neuromuscular block (recovery).

during tetanic stimulation at physiologic frequencies.¹⁸ Of course, more severe residual effects might be found in some patients recovering from anesthesia, but our study did not address this possibility.

During vecuronium block, the geniohyoid muscle has a response to single twitch stimulation that is not distinguishable from that of the thumb,¹⁹ and thus we thought that this degree of block should have been sufficient to indicate potential changes in some of the muscles responsible for upper airway behavior.

The volunteers breathed with a flanged mouthpiece and noseclip. This was necessary because of facial weakness. The influence of these factors on the patency of the upper airway is difficult to estimate. Increased upper airway resistance, such as nasal obstruction, is associated with more obstructive apnea during sleep^{20,21} and sedation.²² Mouth opening increases upper airway collapsibility,²³ but a mouthpiece will reduce oral resistance²⁴ and the presence of a mouthpiece may alter the pattern of activity of the upper airway muscles. Patients who are susceptible to airway obstruction are already likely to be breathing by the oral route.^{25,26} Although this study may not indicate exactly how partial neuromuscular block might affect patients after surgery, we believe this study did provide an indication of how participants might react to this challenge. The volunteers were studied while supine, which favors airway narrowing.²⁷ In addition, we imposed two forms of challenge, increased ventilation and inspiratory resistance, which we believed should exaggerate the possibility of airway collapse. It is possible, however, that in the awake volunteers both of these challenges would increase upper airway muscle activity by reflexes activated either by chemical drive²⁸ or by upper airway

receptors.^{29–32} However, some observations suggest that upper airway sensory receptors in humans have little effect on upper airway muscle activation.³³

Previous studies indicate that airway competence could be impaired during neuromuscular block, which has little effect on respiratory muscle strength, although the effects on other muscles can be profound. Using small bolus doses of d-tubocurarine, Pavlin *et al.*² reduced the inspiratory strength of conscious volunteers (measured as the minimum attainable airway pressure [MIP]) from -90 to -60 $\text{cm H}_2\text{O}$. At this level of block, hand grip strength was reduced by 60%. Head lift and leg raising were impaired when MIP was further reduced to 50% of control. Further neuromuscular block impaired swallowing, caused airway obstruction, and prevented vocal cord closure² despite continued satisfactory resting ventilation.

Upper airway functions such as swallowing, airway support, and airway protection by vocal cord closure require the activities of different muscle groups. Complete vocal cord paralysis requires profound neuromuscular block, and diaphragm and vocal cord adductors have approximately the same degree of sensitivity to nondepolarizing blockade. On the other hand, swallowing can be impaired by small bolus doses of pancuronium (20 $\mu\text{g}/\text{kg}$).³⁴ In the 3 min after the administration of such a dose, the electrical activity of the pharyngeal muscles is reduced to 60%, even though the TOF is 80%. Priming doses of vecuronium (10 or 15 $\mu\text{g}/\text{kg}$) and atracurium (50 or 75 $\mu\text{g}/\text{kg}$) reduce tongue muscle activity during swallowing by 25–60%, despite little or no change in hand grip strength,³⁵ and vecuronium priming doses have been reported to reduce airway integrity despite little change in respiratory volumes.³⁶

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However, during recovery from neuromuscular block, there are no clear differences between the susceptibility of the thumb and the airway muscles, and it appears that the airway difficulties reported after small single doses are transient and at the onset of block, which is more rapid for the tongue than for the thumb.¹⁹ Differences in onset between muscles with different rates of equilibration and sensitivities have been modeled.³⁷ Symptoms reported by volunteers during partial neuromuscular block with mivacurium varied considerably. Jaw weakness was a consistent and prominent sign, and all found swallowing difficult when the TOF was <0.75, but breathing was not affected.³⁸

In clinical practice, it is more relevant to assess the risk of airway obstruction during the period of recovery from a neuromuscular block. The present study shows that this factor, in moderate degree and taken alone, does not increase the risk of airway collapse. We may have chosen to study a degree of neuromuscular block that was just safe: Any more could perhaps precipitate airway collapse, and this could possibly require only a small degree of additional block. In addition, the additional challenge of progressive reduction of pressure at the mouthpiece might have different effects during sleep or sedation. In sleeping adults, airway collapse occurs when airway pressure is reduced^{39,40} by as little as 13 cm H₂O. The response of the respiratory muscles in sleeping persons to airway resistance is less than in the awake state⁴¹ and upper airway responses to airway occlusion during sleep are slow, probably in parallel with changes in chemical drive.⁴² Sedative doses of midazolam cause a large increase in airway resistance.^{17,43} Consequently, the combination of reduced airway muscle strength and impaired consciousness, either by sleep or sedation, may be dangerous even though we have been unable to demonstrate impaired function associated with this degree of partial neuromuscular block in conscious persons.

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