

Neostigmine/Glycopyrrolate Administered after Recovery from Neuromuscular Block Increases Upper Airway Collapsibility by Decreasing Genioglossus Muscle Activity in Response to Negative Pharyngeal Pressure

Frank Herbstreit, Dr.med.,* Daniela Zigrain, Cand.med.,† Christof Ochterbeck, Dipl.-Ing.,‡ Jürgen Peters, Dr.med.,§ Matthias Eikermann, M.D., Ph.D.||

ABSTRACT

Background: Reversal of residual neuromuscular blockade by acetylcholinesterase inhibitors (e.g., neostigmine) improves respiratory function. However, neostigmine may also impair muscle strength. We hypothesized that neostigmine administered after recovery of the train-of-four (TOF) ratio impairs upper airway integrity and genioglossus muscle function.

Methods: We measured, in 10 healthy male volunteers, epiglottic and nasal mask pressures, genioglossus electromyogram, air flow, respiratory timing, and changes in lung volume before, during (TOF ratio: 0.5), and after recovery of the TOF ratio to unity, and after administration of neostigmine 0.03 mg/kg IV (with glycopyrrolate 0.0075 mg/kg). Upper airway critical closing pressure (P_{crit}) was calculated from flow-limited breaths during random pharyngeal negative pressure challenges.

Results: P_{crit} increased significantly after administration of neostigmine/glycopyrrolate compared with both TOF recovery (mean \pm SD, by $27 \pm 21\%$; $P = 0.02$) and baseline (by $38 \pm 17\%$; $P = 0.002$). In parallel, phasic genioglossus activity

evoked by negative pharyngeal pressure decreased (by $37 \pm 29\%$, $P = 0.005$) compared with recovery, almost to a level observed at a TOF ratio of 0.5. Lung volume, respiratory timing, tidal volume, and minute ventilation remained unchanged after neostigmine/glycopyrrolate injection.

Conclusion: Neostigmine/glycopyrrolate, when administered after recovery from neuromuscular block, increases upper airway collapsibility and impairs genioglossus muscle activation in response to negative pharyngeal pressure. Reversal with acetylcholinesterase inhibitors may be undesirable in the absence of neuromuscular blockade.

What We Already Know about This Topic

- ❖ Residual neuromuscular blockade puts patients at risk for respiratory complications, but whether anticholinesterase treatment after spontaneous full recovery alters respiratory neuromuscular function is not known.

What This Article Tells Us That Is New

- ❖ In 10 healthy volunteers, neostigmine with glycopyrrolate reversal after recovery from neuromuscular blockade increased upper airway collapsibility and could have negative respiratory consequences in patients.

* Oberarzt, ‡ Diplom-Ingenieur, Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany. † Medical Student, Universität Duisburg-Essen, Essen, Germany. § Professor of Anesthesiology and Intensive Care Therapy, Universität Duisburg-Essen, and Chairman, Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen. || Privatdozent, Universität Duisburg-Essen, and Assistant Professor, Harvard Medical School, Boston, Massachusetts, and Director of Research Surgical Intensive Care unit, Massachusetts General Hospital, Boston, Massachusetts.

Received from the Klinik für Anästhesiologie & Intensivmedizin, Universität Duisburg-Essen, Essen, Germany, and Universitätsklinikum Essen, Essen, Germany. Submitted for publication January 26, 2010. Accepted for publication August 4, 2010. Support was provided solely from institutional and/or departmental sources. Philips Respiration, Andover, Massachusetts, provided the experimental respirator.

Address correspondence to Dr. Herbstreit: Klinik für Anästhesiologie & Intensivmedizin, Universitätsklinikum Essen, Hufelandstr. 55, D-45122 Essen, Germany. frank.herbstreit@uni-due.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

POSTOPERATIVE residual curarization is common after administration of neuromuscular blocking agents. In the absence of pharmacologic reversal with a cholinesterase inhibitor, postoperative residual curarization occurs in up to 42% of patients receiving vecuronium,^{1,2} in 44% of patients receiving rocuronium,³ and in 57% of patients receiving cisatracurium.³ There is a growing body of evidence that residual neuromuscular blockade places patients at increased risk^{4–8} and may increase costs.⁹

In volunteers, residual neuromuscular blockade impairs airway integrity and puts the upper airway at risk for collapse.⁴ An increased airway collapsibility, despite unaffected values for resting ventilation, may also predispose patients to postoperative respiratory complications,^{6,7} particularly when associated with other airway challenges such as obesity or airway secretions. In addition, difficulty in coordinating swallowing frequently leads

to aspiration.⁸ It is reasonable therefore to reverse residual neuromuscular blockade at the end of anesthesia with neostigmine,¹⁰ a time-honored strategy shown to decrease anesthesia-associated morbidity and mortality.¹¹ Neostigmine reverses neuromuscular blockade by inhibiting cholinesterase, thus increasing the concentration of acetylcholine. Because neostigmine can also induce bradycardia, increased bronchial and pharyngeal secretions, and bronchospasm by muscarinic effects, it is coadministered with an antimuscarinic drug to attenuate such side effects.¹⁰

On the other hand, there is some evidence that neostigmine, when administered in the absence of neuromuscular transmission block, may impair evoked peripheral skeletal muscle strength in humans^{12,13} and upper airway dilator muscle function in animals,^{14,15} possibly by depolarizing neuromuscular block,¹² acetylcholine receptor desensitization,¹⁶ or by open-channel block.¹⁷

We therefore hypothesized that administration of neostigmine after spontaneous recovery from nondepolarizing neuromuscular blockade increases upper airway collapsibility and decreases genioglossus muscle activation in response to negative pharyngeal pressure challenges in healthy, awake volunteers.

Materials and Methods

Subjects

After approval of the local institutional review board (Faculty of Medicine, University of Duisburg-Essen, Germany) and written informed consent, we studied 10 healthy (American Society of Anesthesiologists physical status 1) male volunteers (mean \pm SD; age, 34 ± 6 yr; weight, 82 ± 13 kg; height, 181 ± 7 cm). All volunteers were nonsmokers. Those with a history of surgery to the pharynx, chronic obstructive pulmonary disease, or other airway pathology were excluded. The volunteers had no signs and symptoms of obstructive sleep apnea (habitual snoring or interrupted nocturnal breathing as reported by the spouse or roommate), excessive daytime sleepiness, or arterial hypertension, and the STOP BANG questionnaire¹⁸ did not suggest a high risk for obstructive sleep apnea. All experiments were conducted at the University Medical Center of the Universität Duisburg-Essen in a laboratory equipped with anesthesia workstation and resuscitation equipment. A board-certified anesthesiologist was present throughout all experiments for safety reasons. Standard anesthesia monitoring (electrocardiogram, pulse oximetry, capnography, and oscillometric blood pressure measurements) was used continuously in addition to the measurements performed for study reasons. The volunteers had been trained to breathe *via* a tight-fitting nasal mask and were used in the experimental setup described below. The subjects were blind to the timing of drug administration and the intent of the study.

Measurements

To assess the critical closing pressure of the upper airway (Pcrit), we used an experimental respirator (Pcrit 3000; Re-

spironics, Inc., Murrysville, PA) to generate positive and negative airway pressures. The pressure within the nasal mask (upstream pressure) was measured using a differential pressure transducer (MP45; Validyne Engineering, Northridge, CA) *via* a dedicated port in the mask. Epiglottic (downstream) pressure was measured using a custom-made catheter tip manometer (Millar Instruments, Houston, TX) calibrated in warm (37°C) saline before placement. This catheter was placed *via* a decongested (0.3 ml oxymetazoline 0.05%; Novartis, Munich, Germany) and anesthetized (0.5 ml lidocaine 4%; Astra Chemicals, Wedel/Holstein, Germany) nostril and advanced until the tip of the catheter, when observed through the volunteer's open mouth, just disappeared behind the base of the tongue. Respiratory flow was measured using a pneumotachograph (Model 3830; Hans Rudolph, Kansas City, MO) with a DC-amplifier (MIO-0501; FMI, Seeheim, Germany) and a differential pressure transducer (Model DP45-32 with CD15 carrier demodulator; Validyne Engineering) connected to the mask. The pneumotachograph was calibrated with a large-volume (2 l) syringe.

To assess Pcrit, mask pressure was randomly dropped from baseline pressure (+2 cm H₂O) to pressures between -2 and -30 cm H₂O for four breaths and then returned to baseline pressure. Intervals of at least 1 min with baseline pressure prevailing were interposed between negative pressure challenges. Twelve random pressure drops were performed with at least 1 min of baseline pressure interposed. Accordingly, one measurement of Pcrit took approximately 15 min. Thus, our Pcrit values reflect airway collapsibility during this time. Pcrit was calculated from the flow-limited breaths, as described previously.^{4,19} Flow limitation was defined as unchanged inspiratory flow despite a further decrease of pharyngeal (epiglottic) pressure²⁰ and a flattened flow tracing in a flow-time plot.²¹ Mask pressure was then plotted against maximum inspiratory flow for the flow-limited breaths and fitted using linear regression. Pcrit was assumed to be the pressure at which the flow equaled zero in the linear regression graph. We had previously tested the reproducibility of our Pcrit measurement technique in four awake volunteers on two different study days and found an acceptable consistency of 90%. A representative Pcrit calculation from one volunteer is shown in figure 1.

The genioglossus muscle electromyogram was measured *via* 32-gauge hook-wire electrodes of 50 mm length (Viasys Healthcare, Hoechberg, Germany) inserted transcutaneously into the genioglossus muscle *via* a 26-gauge needle using ultrasound guidance. The electrodes were referenced to a ground electrode placed on the upper arm. The electromyogram signal was filtered (band-pass filter, 30–1,000 Hz), amplified, and rectified (Grass amplifier G62C-3; Grass Technologies, West Warwick, RI). The filtered and rectified signal was further filtered using moving time averaging (time constant, 100 ms). The amplifier was adjusted to yield a full-scale deflection when the volunteer pressed his tongue with maximum strength against his teeth with the mouth closed. The amplitude of the moving time average recorded

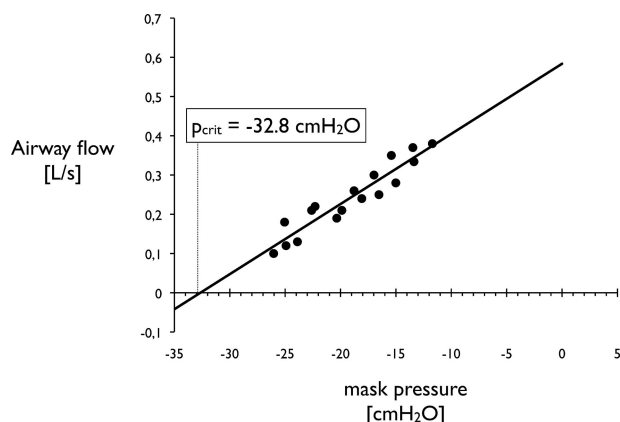


Fig. 1. Method of calculation of upper airway critical closing pressure (P_{crit}) by linear regression in a volunteer. Air flow is plotted as a function of mask pressure. During a total of 17 random pressure drops, flow limitation was observed. Values derived from these flow-limited breaths were used for analysis and extrapolated to P_{crit} (mask pressure at zero flow) by linear regression.

during the second and third breath of a four breath negative pressure challenge were averaged and used to quantify the genioglossus electromyogram.

Tidal volume and variables of respiratory timing were measured by respiratory inductance plethysmography (LifeShirt; VivoMetrics, Ventura, CA).²² The transducers were fitted according to the manufacturer's sizing chart and calibrated using a fixed-volume bag and the calibration protocol provided.²³ Data were digitally recorded (LifeShirt200 recorder; VivoMetrics), stored on a memory card, and processed on a computer (VivoLogic V 3.1 software; VivoMetrics). Respiratory rate, inspiratory and expiratory time, tidal volume and its ratio to inspiratory time (V_t/T_i), inspiration to expiration ratio (I:E), and changes in end-expiratory lung volume were averaged from 20 breaths preceding the mask pressure drop maneuvers.

The degree of neuromuscular blockade was measured continuously by accelerometry of the adductor pollicis muscle and ulnar nerve stimulation (TOF-watch SX; Schering-Plough, Kenilworth, NJ).²⁴ The skin was prepared with an abrasive paste (NuPrep Gel, D.O. Weaver, Aurora, CO), cleaned with ethanol 80%, and dried with gauze. We randomly used the volunteers' right ($n = 5$) or left ($n = 5$) ulnar nerve for stimulation. Two stimulation surface electrodes (PNS electrode; NDM, Dayton, OH) were placed over the ulnar nerve with one electrode positioned on the ulnar side of the flexor carpi radialis tendon and the other one positioned 3 cm proximal to the first. The transducer was positioned with the flat side against the thumb. Supramaximal stimulation current was determined with a 5-mA increase in stimulation current during five consecutive stimuli increasing twitch height by less than 5%. This was checked twice, and this stimulation current was used subsequently for measurements, providing a stable signal. During a subsequent 30-min period used for signal stabilization before baseline mea-

surements, we applied single-twitch stimulation, during which an increasing response was observed (staircase phenomenon). The TOF-watch SX was then calibrated using the CAL 1 sequence²⁵ to set the T1 response to 100% (baseline). Stimulation was then continued in the TOF mode, and supramaximal stimulation current was applied throughout the experimental protocol. The data obtained by the TOF-watch SX were transferred to and stored in a computer using the TOF-link interface and the TOF-watch SX monitoring software (Schering-Plough).

Pressure and flow signals were recorded in parallel on digital tape (Model RD 200 T; TEAC, Wiesbaden-Erbenheim, Germany) and with a digital recording system (Powelab 16/38; ADInstruments, Colorado Springs, CO), and also documented on a thermarray recorder (Dash 16; AstroMed, West Warwick, RI). Data were assessed using Chart 4.0 software (ADInstruments). For safety reasons, arterial oxygen saturation (digit II) and expiratory carbon dioxide-concentration (sample port in the nasal mask) were monitored (PM8050; Dräger, Lübeck, Germany).

Experimental Protocol

Following the instrumentation described above, a nasal mask was administered and held in place with a head strap. With the calibrated transducers in place each volunteer was asked to perform the following maneuvers: (1) to swallow several times, (2) to push the tongue against the front teeth as hard as possible several times, and (3) to inspire as hard as possible several times while the inspiratory line of the airway was occluded. Baseline measurements of P_{crit} were then performed, as described above.

After baseline measurements, 0.1 mg/kg rocuronium (Essex Pharma GmbH, Munich, Germany) was injected and followed by a continuous infusion (10–80 mg/h), as guided by TOF measurements. When steady-state conditions were achieved at a target TOF ratio of 0.5, rocuronium infusion was adjusted to maintain a neuromuscular blockade of that degree for at least 5 min before further measurements were performed. A TOF-ratio range of 0.45–0.55 (deviation of up to 10%) was considered acceptable and all measurements were performed within that range. After measurements had been performed, the rocuronium infusion was terminated. After return of the TOF ratio to unity, another series of measurements was performed.

Neostigmine (0.03 mg/kg; DeltaSelect, Pfullingen, Germany) and glycopyrrolate (0.0075 mg/kg; Riemser, Greifswald, Germany) were then administered together intravenously, and a series of measurements was initiated 2 min later and concluded approximately 17 min after neostigmine/glycopyrrolate injection. For assessment of airway collapsibility at a more closely defined point of time (*i.e.*, 15 min after neostigmine injection), we also recorded air flow, mask pressure, and genioglossus electromyogram during minute 13 of the random pressure drop series, and applied and analyzed peak inspiratory air flow observed at the lowest mask pressure applied during minute 15 after administration of the reversal agent.

Statistical Analysis

Data are presented as mean \pm SD unless otherwise specified. Statistical analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, IL). We tested the *a priori* hypotheses that after administration of neostigmine/glycopyrrolate, (1) Pcrit is less negative than after spontaneous recovery of neuromuscular blockade (primary criterion) and (2) electromyogram activity of the genioglossus muscle in response to negative pharyngeal pressure is decreased (secondary criterion). Differences in Pcrit between baseline and after administration of neostigmine/glycopyrrolate were compared with a Student *t* test for paired samples. Based on our previous study on the effects of partial neuromuscular blockade on genioglossus electromyogram,⁴ we estimated (paired *t* test) that 10 volunteers would provide an 80% power to detect, with an α error

P of 0.05 (two-tailed testing), a change in critical airway closing pressure of 10% with an SD of 10% after administration of neostigmine/glycopyrrolate.

We selected the genioglossus electromyogram as a secondary criterion to be tested only if significant results in testing the primary criterion were obtained.²⁶ We used a linear mixed model for repeated measures (compound symmetry repeated covariance type), including neuromuscular function (baseline, TOF ratios of 0.5, unity, and after administration of neostigmine/glycopyrrolate) and mask pressure (from +2 to -30 cm H₂O) as repeated variables. First, all data (10 volunteers, 3 levels of neuromuscular function; TOF = 0.5 at recovery, TOF = 1 after neostigmine; 7 levels of mask pressure = 210 data points) were entered into the model to test for an effect on genioglossus activity of neuro-

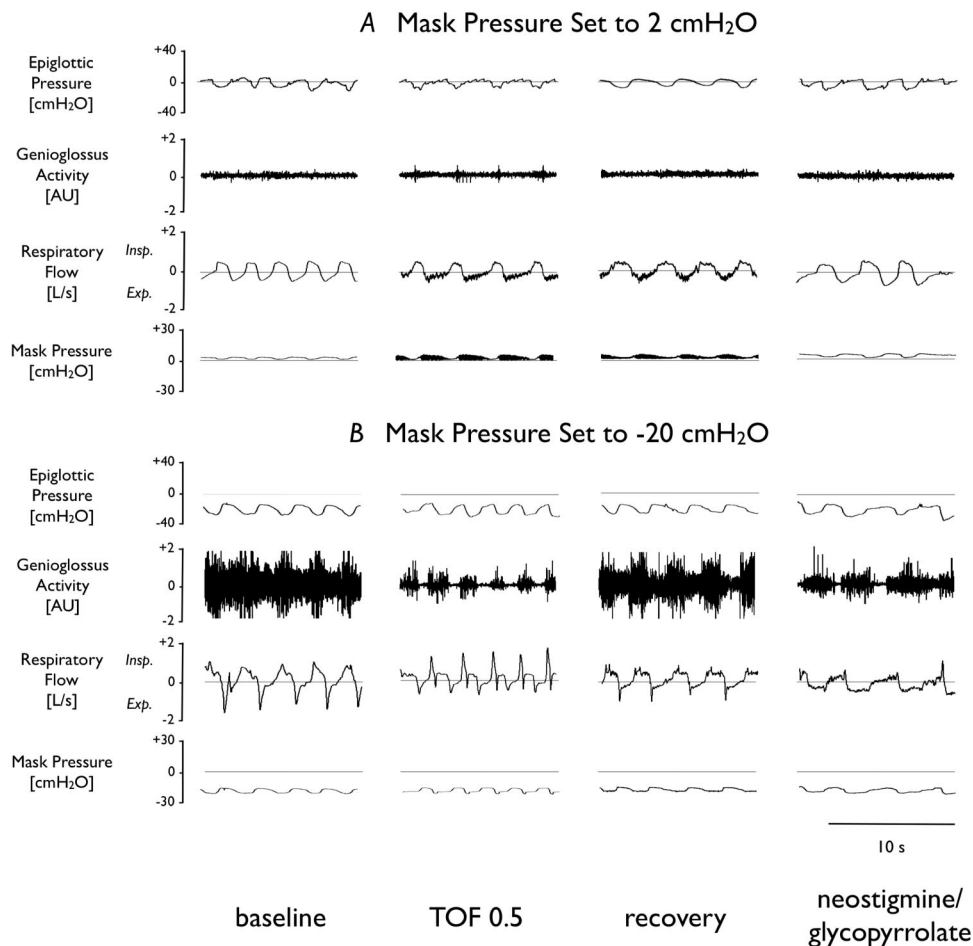


Fig. 2. Representative recording of main variables from an awake healthy volunteer before partial neuromuscular blockade (baseline), during impaired neuromuscular transmission with a target train-of-four (TOF) ratio of 0.5, after spontaneous recovery of the TOF ratio to unity, and during measurements initiated 2 min after injection of neostigmine (0.03 mg/kg) and glycopyrrolate (0.0075 mg/kg). (A) Mask pressure at 2 cm H₂O. Phasic (respiratory) genioglossus activity is very low while breathing near atmospheric pressure. During impaired neuromuscular transmission, no flow limitation is observed at this mask pressure. (B) Same volunteer during a negative pressure challenge (-20 cm H₂O). Before partial neuromuscular blockade, phasic genioglossus activity is markedly increased compared with breathing near atmospheric pressure. During partial neuromuscular blockade, phasic genioglossus activity is markedly increased compared with breathing at atmospheric pressure. However, the magnitude of the compensatory increase in genioglossus activity in response to negative pharyngeal pressure is impaired, and flow limitation is observed. After spontaneous recovery of the TOF ratio to unity, the compensatory phasic genioglossus activity is restored. Injection of neostigmine/glycopyrrolate attenuates the increase in genioglossus activity, and the changes observed attain similar values as those seen with partial neuromuscular blockade with a TOF ratio of 0.5.

muscular function and of mask pressure. In the second step, we tested for specific differences in genioglossus activity between values after neostigmine/glycopyrrolate administration and recovery from neuromuscular blockade. Scheffé test was applied for conducting *post hoc* comparisons. All other comparisons were made with an exploratory intention.

Results

A representative panel of one volunteer's recording is given in figure 2.

Critical Airway Closing Pressure

Pcrit averaged -54.7 ± 18.7 cm H₂O (mean \pm SD) at baseline before neuromuscular blockade and significantly ($P = 0.001$) increased (to less negative values) by $54 \pm 4.4\%$ during partial neuromuscular blockade (TOF ratio: 0.5, $P = 0.001$). Pcrit was still increased by 16% ($P = 0.01$) after the TOF ratio had returned to unity (recovery).

Pcrit increased significantly after administration of neostigmine/glycopyrrolate compared with either recovery (*i.e.*, before neostigmine/glycopyrrolate administration) (by $27 \pm 21\%$; $P = 0.02$) or baseline (by $38 \pm 17\%$; $P = 0.002$) measurements (fig. 3).

Genioglossus Muscle Activity

Phasic genioglossus activity increased with negative airway pressure ($P = 0.0001$). It almost quadrupled when a negative airway pressure of -20 cm H₂O was applied under baseline conditions. This compensatory response to a negative pharyngeal pressure challenge was blunted with partial neuromuscular blockade (TOF ratio: 0.5). Return of neuromus-

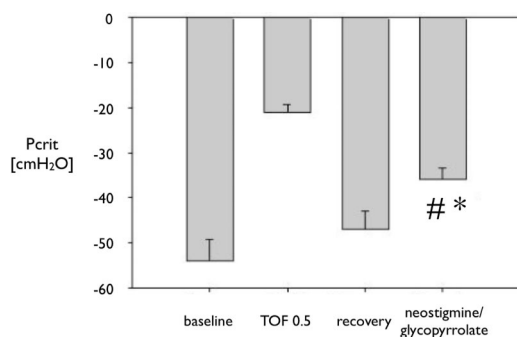


Fig. 3. Upper airway critical closing pressure (Pcrit) in awake healthy volunteers at baseline before neuromuscular blockade, with impaired neuromuscular transmission and a target train-of-four (TOF) ratio of 0.5, after spontaneous recovery of the TOF ratio to unity, and after injection of neostigmine/glycopyrrolate. Upper airway closing pressure significantly increased during partial neuromuscular blockade and was still abnormal even with recovery of the TOF ratio to unity (*i.e.*, before injection of neostigmine/glycopyrrolate) ($P = 0.01$ vs. baseline). However, upper airway closing pressure significantly increased after injection of neostigmine/glycopyrrolate. Data are mean \pm SD from 10 awake volunteers. * $P = 0.002$ versus baseline; # $P = 0.02$ versus recovery.

cular function restored the genioglossus muscle response to negative airway pressure to almost baseline values.

After the injection of neostigmine/glycopyrrolate, phasic genioglossus activity was markedly impaired when negative airway pressure was applied ($P = 0.005$, fig. 4). Fifteen minutes after neostigmine/glycopyrrolate administration, effects on upper airway function remained significant. During pressure drops at this time (mean, -16.5 cm H₂O \pm 8.5), genioglossus activity was decreased by $39.8 \pm 26\%$ ($P = 0.015$) and the peak inspiratory airflow decreased by $22.9 \pm 50\%$ relative to levels during equivalent pressure drops at baseline.

Effects on Lung Volume and Other Respiratory Variables

Neostigmine/glycopyrrolate did not affect respiratory timing (I:E ratio, 0.56 ± 0.16 [TOF recovery] vs. 0.57 ± 0.17 [after neostigmine/glycopyrrolate, $P = 0.5$]), respiratory rate (13.8 ± 3.8 vs. 13.4 ± 3.2 min⁻¹, $P = 0.6$), tidal volume (316 ± 109 vs. 324 ± 108 ml, respectively, $P = 0.55$), Vt/Ti (406 ± 31 vs. 411 ± 36 ml/s, respectively, $P = 0.3$), or end-expiratory lung volume. The respiratory variables are presented in table 1.

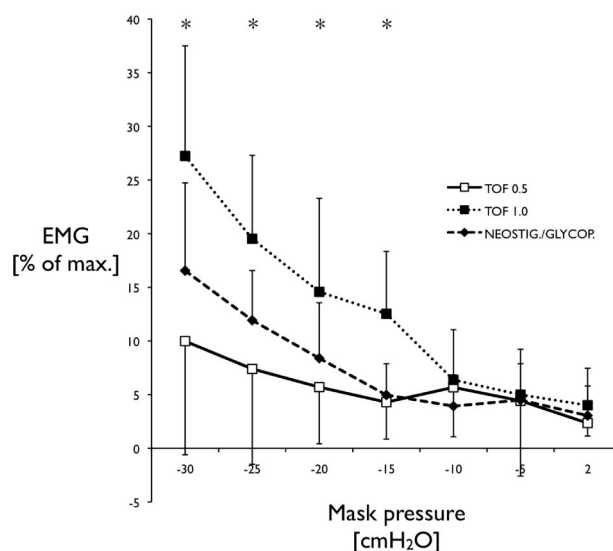


Fig. 4. Genioglossus muscle activity as a function of negative mask pressure with neuromuscular blockade at a target TOF ratio of 0.5 (open squares), after spontaneous recovery of the TOF ratio to unity (solid squares), and after injection of neostigmine/glycopyrrolate. The genioglossus activity is presented as a percentage of maximal activity (observed when the volunteer pressed his tongue with maximum strength against his teeth with the mouth closed). Genioglossus activity evoked in response to negative pressure challenges is impaired with neuromuscular blockade. The compensatory genioglossus response to a pressure drop is restored after return of the TOF ratio to unity. After administration of neostigmine/glycopyrrolate, genioglossus activity in response to negative airway pressure is markedly and significantly decreased. Data are mean \pm SD from 10 volunteers. * $P = 0.005$ neostigmine/glycopyrrolate versus recovery (*i.e.*, before injection of neostigmine/glycopyrrolate, same mask pressure). EMG = genioglossus electromyogram; TOF = train of four.

Table 1. Respiratory Variables

	Arterial Oxygen Saturation [%]	End-Tidal pCO ₂ [mmHg]	I:E-ratio	Respiratory Rate [min ⁻¹]	Tidal Volume [ml]
Baseline	98.3 ± 1.1	36.6 ± 1.9	0.60 ± 0.15	13.1 ± 4.2	345 ± 122
TOF-ratio 0.5	98.3 ± 0.9	36.3 ± 1.6	0.59 ± 0.19	14.0 ± 3.5	336 ± 112
Recovery	98.1 ± 1.0	36.7 ± 1.8	0.56 ± 0.16	13.8 ± 3.8	316 ± 109
Neostigmine/glycopyrrolate	98.5 ± 1.1	36.4 ± 2.0	0.57 ± 0.17	13.4 ± 3.2	324 ± 108

Respiratory variables obtained from 10 healthy volunteers before, during, and after neuromuscular blockade, and following injection of neostigmine/glycopyrrolate at a TOF ratio of unity. Data are mean ± SD.

I:E-ratio = ratio of inspiratory time and expiratory time; pCO₂ = partial pressure of carbon dioxide; TOF-ratio = train-of-four ratio.

Effects on Evoked Adductor Pollicis Muscle Function

Neostigmine/glycopyrrolate administered after recovery of the TOF ratio to unity (1.05 ± 0.03) did not alter the TOF ratio (1.05 ± 0.04 ; $P = 0.89$) or twitch height (0.94 ± 0.15 ; $P = 0.43$) 2 min after administration. Seven minutes after neostigmine/glycopyrrolate administration, TOF ratio (1.06 ± 0.06 ; $P = 0.85$) and twitch height (0.95 ± 0.17 ; $P = 0.40$) were still unchanged.

Clinical Effects

After neostigmine/glycopyrrolate administration, all volunteers ($n = 10$) reported difficulty to swallow normally and showed muscle fasciculation. Five volunteers complained of diplopia. At the end of the study, all volunteers reported complete recovery from these signs and symptoms of partial neuromuscular transmission failure.

Discussion

Administration of neostigmine/glycopyrrolate, when administered after spontaneous recovery of neuromuscular function, in a dose similar to that recommended, and in routine clinical use, led to a significant increase in Pcrit and thus increased airway collapsibility in healthy volunteers. The increase in airway collapsibility was of a magnitude comparable with neuromuscular blockade with a TOF ratio of 0.5. Furthermore, the normal compensatory activation of the genioglossus muscle in response to airway negative pressure challenges was blunted after administration of neostigmine/glycopyrrolate (*i.e.*, neostigmine/glycopyrrolate evoked a significant impairment of upper airway dilator muscle function). Accordingly, whereas previous studies demonstrated airway compromise with residual neuromuscular blockade and thus a probable clinical need for reversal agents, the results of this study reveal increased airway collapsibility as a result of neostigmine/glycopyrrolate, if given after recovery from neuromuscular transmission blockade.

Reversal of residual neuromuscular blockade is an important goal in regard to patient safety because it is associated with a decreased risk of 24-h postoperative morbidity and mortality.¹¹ Omitting reversal introduces a significant risk of residual paralysis, even with short-acting neuromuscular blocking agents.²⁷ However, in healthy volunteers, if neostigmine/glycopyrrolate is administered at a TOF ratio of unity, Pcrit significantly increases whereas genioglossus ac-

tivity decreases. The marked impairment of genioglossus muscle function and the increased upper airway collapsibility observed in volunteers may indicate an increased risk of airway collapse in patients after extubation, if the effects of neostigmine are being added to the airway-collapsing effects of anesthetic agents²⁸ and/or mechanical obstruction.²⁹ Furthermore, although we did not assess Pcrit later in the time course after neostigmine/glycopyrrolate administration, the decrease of genioglossus electromyogram observed even 15 min after injection of neostigmine/glycopyrrolate suggests impairment of airway integrity for at least 15 min (*i.e.*, in a clinically relevant time frame).

Accordingly, our data suggest that administration of reversal agents should optimally be guided by evaluation of the TOF ratio, because in the absence of quantitative neuromuscular monitoring, it is difficult to ascertain whether residual block still exists. Unfortunately, quantitative neuromuscular transmission monitoring is not uniformly applied in clinical practice.^{30,31} Thus, cholinesterase inhibitors are often routinely administered by clinicians at the end of anesthesia to reverse suspected effects of neuromuscular blocking agents regardless of whether such residual effects are present or not. Our data also imply that no unwarranted reversal by cholinesterase inhibitors should be performed (*i.e.*, reversal after neuromuscular function has recovered to a TOF ratio of unity).

It has recently been suggested that 30 µg/kg neostigmine is sufficient for reversal of neuromuscular blockade, if the patient has four equal responses to TOF stimulation.³² Our data suggest that even neostigmine 30 µg/kg administered after recovery of the TOF ratio may put a patient at risk for impaired upper airway integrity. Accordingly, we believe that routine use of even smaller doses of cholinesterase inhibitors when no fade is appreciable in the TOF maneuver requires that quantitative monitors be available to assess the existence of residual neuromuscular block as well as complete recovery of neuromuscular function. Administration of reversal agents making use of another pharmacologic mechanism, such as sugammadex, may not be a threat to airway integrity,¹⁵ but this will require studies in humans. The effect on upper airway patency of neostigmine/glycopyrrolate observed in our healthy, awake volunteers is in line with data obtained in anesthetized rats,¹⁴ suggesting clinical significance of these animal data.

Effects of neuromuscular blocking drugs are muscle dependent,³³ and it has been suggested that upper airway dila-

tor muscles are particularly susceptible to low doses of nondepolarizing neuromuscular blocking agents.^{8,34} We found that doses of neostigmine/glycopyrrolate that affected neither the TOF ratio nor the twitch height of the adductor pollicis muscle nonetheless markedly impaired genioglossus muscle function and potentially increased airway collapsibility. This suggests that the upper airway muscles may also be vulnerable to an overabundance of acetylcholine at the neuromuscular junction.

It is possible that TOF-ratio measurements are not sensitive enough to detect small degrees of skeletal muscle dysfunction from partial paralysis.^{35,36} Indeed, decreases in upper esophageal sphincter resting tone,⁸ peak inspiratory flow,³⁷ and end-inspiratory upper airway volume³⁸ occur in some volunteers recovering from neuromuscular blockade, even with recovery of the TOF ratio to 0.9–1.^{8,37,38} Neuromuscular blocking drugs (both nondepolarizing and depolarizing compounds) evoke a progressive failure of neuromuscular transmission as documented using increasing rates of nerve stimulation.^{39,40} The TOF stimulation uses a stimulation frequency of 2 Hz, whereas the firing frequency of the hypoglossal nerve (innervating the genioglossus muscle) during normal inspiration is much higher (15–25 Hz).⁴¹ Thus, decreases in genioglossus activity during partial paralysis may exist even when adductor pollicis muscle TOF ratio and twitch height are normal. This might explain why the genioglossus muscle electromyogram in response to negative pharyngeal pressure challenges was abnormal after neostigmine/glycopyrrolate, whereas the adductor pollicis muscle response to TOF stimulation was not.

With the TOF ratio recovered to unity, we observed a Pcrit less negative than at baseline. This result is likely due to residual effects of rocuronium undetectable by measurement of the TOF ratio, and this is in line with our previous studies.^{4,36}

The mechanisms proposed for the effects of cholinesterase inhibitors on neuromuscular transmission include desensitization of acetylcholine receptors,¹⁶ depolarization block,¹² or open channel block.¹⁷ Neuromuscular blocking agents also have effects on carotid body chemoreceptor responses that are reversible with neostigmine,⁴² and an impaired respiratory drive due to neostigmine/glycopyrrolate has to be considered. However, V_t/T_i did not change significantly over the course of the protocol, suggesting an unchanged respiratory drive. Neostigmine-induced muscarinic side effects on the upper or bronchial airways have not been observed when the drug is coadministered with an antimuscarinic agent even in asthmatic patients.⁴³

We applied neostigmine/glycopyrrolate at recovery of the TOF ratios to unity, and it would be interesting to study in humans whether neostigmine, when given during slight impairment of the TOF ratio (0.5–0.8), increases or decreases airway collapsibility. In rats, reversal with neostigmine at a TOF ratio of 0.5 or 0.8 improves genioglossus electromyogram,¹⁵ suggesting beneficial effects of neostigmine reversal of subtle neuromuscular blockade on upper airway collapsibility, in contrast to its effects when applied after recovery of the TOF ratio to unity.

Limitations

The technique applied to assess Pcrit is typically applied during sleep or anesthesia.^{44,45} Measurements of Pcrit in awake volunteers may be more prone to artifacts. We have previously performed reliable Pcrit measurements in awake volunteers.⁴ In addition, our data show that effects of partial neuromuscular blockade on Pcrit compare well to the effects on airway size during inspiration at the same level of partial neuromuscular blockade.³⁸ In future studies, it would be interesting to add peripheral muscle strength measurement to the measurement set-up, such that the volunteers' effort, an important variable for measurements of Pcrit in awake volunteers, can also be assessed.

Neostigmine and glycopyrrolate were administered together to mimic their routine clinical use. Whether neostigmine alone would have a similar effect has not been assessed in our study. In animal experiments, however, antimuscarinic drugs (glycopyrrolate or atropine) alone had no effect on the upper airway, whereas neostigmine together with either atropine or glycopyrrolate impaired genioglossus muscle function.^{14,15}

Our study does not allow comments on the further time course of neostigmine's effect on upper airway collapsibility. We measured changes in Pcrit and genioglossus muscle function during a 15-min interval after neostigmine injection. This interval was technically required to calculate Pcrit. The time frame was also chosen based on our previous observations in pilot studies in volunteers (unpublished data, Matthias Eikermann, Privatdozent Dr.med., and Juergen Peters, Prof. Dr.med., Universitätsklinikum Essen, Essen, Germany, November 2008), measuring flow-volume characteristics 5, 10, 15, and 20 min after neostigmine/atropine administration. We found that forced inspiratory volume in 1 s and peak inspiratory flow were impaired within 5 min after injection and that these effects were still present 20 min after administration. In addition, our animal data show that neostigmine's effect at the genioglossus electromyogram peaks within 2 min after injection, and this effect remains significant for at least 15 min.¹⁵

We did not establish a dose-response relationship for the effect of neostigmine/glycopyrrolate on the upper airway. Accordingly, no assumptions can be made about a safe dose of these reversal agents when given after recovery of the TOF ratio. Fuchs-Buder *et al.*⁴⁶ recently observed that low doses of neostigmine (20–30 $\mu\text{g/kg}$) are effective in reversing a shallow neuromuscular blockade, reflecting the dose administered in our study.

In conclusion, neostigmine/glycopyrrolate given after spontaneous recovery of neuromuscular function to an adductor pollicis TOF ratio of unity, increases upper airway collapsibility and impairs the genioglossus electromyogram in response to negative pharyngeal pressure. Thus, reversal with acetylcholinesterase inhibitors may be undesirable in the absence of neuromuscular blockade.

The authors thank David P. White, M.D., Clinical Professor of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, for providing useful advice.

References

- Baillard C: [Incidence and complications of post operative residual paralysis.] *Ann Fr Anesth Reanim* 2009; 28(suppl 2):S41-5
- Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M: Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; 84:394-5
- Maybauer DM, Geldner G, Blobner M, Pühringer F, Hofmockel R, Rex C, Wulf HF, Eberhart L, Arndt C, Eikermann M: Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia* 2007; 62:12-7
- Herbstreit F, Peters J, Eikermann M: Impaired upper airway integrity by residual neuromuscular blockade: Increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *ANESTHESIOLOGY* 2009; 110:1253-60
- Murphy GS: Residual neuromuscular blockade: Incidence, assessment, and relevance in the postoperative period. *Minerva Anesthesiol* 2006; 72:97-109
- Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS: Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; 107:130-7
- Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. *ANESTHESIOLOGY* 2008; 109:389-98
- Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI: The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: Pharyngeal videoradiography and simultaneous manometry after atracurium. *ANESTHESIOLOGY* 2000; 92:977-84
- Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U: Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. *Br J Anaesth* 2010; 105:304-9
- Kopman AF, Eikermann M: Antagonism of non-depolarising neuromuscular block: Current practice. *Anaesthesia* 2009; 64(suppl 1):22-30
- Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
- Payne JP, Hughes R, Al Azawi S: Neuromuscular blockade by neostigmine in anesthetized man. *Br J Anaesth* 1980; 52:69-76
- Caldwell JE: Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. *Anesth Analg* 1995; 80:1168-74
- Eikermann M, Fassbender P, Malhotra A, Takahashi M, Kubo S, Jordan AS, Gautam S, White DP, Chamberlin NL: Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. *ANESTHESIOLOGY* 2007; 107:621-9
- Eikermann M, Zaremba S, Malhotra A, Jordan AS, Rosow C, Chamberlin NL: Neostigmine but not sugammadex impairs upper airway dilator muscle activity and breathing. *Br J Anaesth* 2008; 101:344-9
- Yost CS, Maestroni E: Clinical concentrations of edrophonium enhance desensitization of the nicotinic acetylcholine receptor. *Anesth Analg* 1994; 78:520-6
- Legendre P, Ali DW, Drapeau P: Recovery from open channel block by acetylcholine during neuromuscular transmission in zebrafish. *J Neurosci* 2000; 20:140-8
- Abrishami A, Khajehdehi A, Chung F: A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth* 2010; 57:423-38
- Jordan AS, Wellman A, Edwards JK, Schory K, Dover L, MacDonald M, Patel SR, Fogel RB, Malhotra A, White DP: Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Appl Physiol* 2005; 99:2020-7
- Jordan AS, Wellman A, Heinzer RC, Lo YL, Schory K, Dover L, Gautam S, Malhotra A, White DP: Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. *Thorax* 2007; 62:861-7
- Isono S, Morrison DL, Launois SH, Feroah TR, Whitelaw WA, Remmers JE: Static mechanics of the velopharynx of patients with obstructive sleep apnea. *J Appl Physiol* 1993; 75:148-54
- Wilhelm FH, Roth WT, Sackner MA: The lifeShirt. An advanced system for ambulatory measurement of respiratory and cardiac function. *Behav Modif* 2003; 27:671-91
- Kent L, O'Neill B, Davison G, Nevill A, Elborn JS, Bradley JM: Validity and reliability of cardiorespiratory measurements recorded by the LifeShirt during exercise tests. *Respir Physiol Neurobiol* 2009; 167:162-7
- Claudius C, Viby-Mogensen J: Acceleromyography for use in scientific and clinical practice: A systematic review of the evidence. *ANESTHESIOLOGY* 2008; 108:1117-40
- Schering-Plough TOF-watch SX Operator manual. Whitehouse Station, NJ, Schering-Plough
- Bauer P: Multiple testing in clinical trials. *Stat Med* 1991; 10:871-89
- Tramèr MR, Fuchs-Buder T: Omitting antagonism of neuromuscular block: Effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. *Br J Anaesth* 1999; 82:379-86
- Hillman DR, Walsh JH, Maddison KJ, Platt PR, Kirkness JP, Noffsinger WJ, Eastwood PR: Evolution of changes in upper airway collapsibility during slow induction of anesthesia with propofol. *ANESTHESIOLOGY* 2009; 111:63-71
- Williamson JP, Phillips MJ, Hillman DR, Eastwood PR: Managing obstruction of the central airways. *Intern Med J* 2010; 40:399-410
- Cammu G, De Witte J, De Veylder J, Byttebier G, Vandepuit D, Foubert L, Vandenbroucke G, Deloof T: Postoperative residual paralysis in outpatients *versus* inpatients. *Anesth Analg* 2006; 102:426-9
- Foster JG, Kish SK, Keenan CH: National practice with assessment and monitoring of neuromuscular blockade. *Crit Care Nurs Q* 2002; 25:27-40
- Lien CA: Neostigmine: How much is necessary for patients who receive a nondepolarizing neuromuscular blocking agent? *ANESTHESIOLOGY* 2010; 112:16-8
- Hemmerling TM, Schmidt J, Hanusa C, Wolf T, Schmitt H: Simultaneous determination of neuromuscular block at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscles. *Br J Anaesth* 2000; 85:856-60
- Isono S, Kochi T, Ide T, Sugimori K, Mizuguchi T, Nishino T: Differential effects of vecuronium on diaphragm and geniohyoid muscle in anesthetized dogs. *Br J Anaesth* 1992; 68:239-43
- Waud BE, Waud DR: The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. *ANESTHESIOLOGY* 1971; 35:456-64
- Eikermann M, Gerwig M, Hasselmann C, Fiedler G, Peters J: Impaired neuromuscular transmission after recovery of the train-of-four ratio. *Acta Anaesthesiol Scand* 2007; 51:226-34
- Eikermann M, Groeben H, Hüsing J, Peters J: Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. *ANESTHESIOLOGY* 2003; 98:1333-7
- Eikermann M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, de Greiff A, Peters J: The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med* 2007; 175:9-15
- Gissen AJ, Katz RL: Twitch, tetanus and posttetanic potentiation as indices of nerve-muscle block in man. *ANESTHESIOLOGY* 1969; 30:481-7

40. Churchill-Davidson HC, Christie TH: The diagnosis of neuromuscular block in man. *Br J Anaesth* 1959; 31: 290-301
41. Saboisky JP, Gorman RB, De Troyer A, Gandevia SC, Butler JE: Differential activation among five human inspiratory motoneuron pools during tidal breathing. *J Appl Physiol* 2007; 102:772-80
42. Jonsson M, Kim C, Yamamoto Y, Runold M, Lindahl SG, Eriksson LI: Atracurium and vecuronium block nicotine-induced carotid body chemoreceptor responses. *Acta Anaesthesiol Scand* 2002; 46:488-94
43. Bourgain JL, Debaene B, Meistelman C, Donati F: Respiratory mechanics in anaesthetised patients after neostigmine-atropine. A comparison between patients with and without chronic obstructive pulmonary disease. *Acta Anaesthesiol Scand* 1993; 37:365-9
44. Litman RS, McDonough JM, Marcus CL, Schwartz AR, Ward DS: Upper airway collapsibility in anesthetized children. *Anesth Analg* 2006; 102:750-4
45. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S: Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol* 1988; 64:789-95
46. Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F: Antagonism of low degrees of atracurium-induced neuromuscular blockade: Dose-effect relationship for neostigmine. *ANESTHESIOLOGY* 2010; 112:34-40

ANESTHESIOLOGY REFLECTIONS

Gillray Etches *New Discoveries in PNEUMATICKS!*



Scientific Researches! — New Discoveries in PNEUMATICKS! — or — an Experimental Lecture on the Powers of Air

Published in 1802, *Scientific Researches! — New Discoveries in PNEUMATICKS! or, Experimental Lecture on the Powers of Air* was created by James Gillray (died 1815). In this etching, he caricatured a lecturer—most likely physician and chemist Thomas Garnett (1766–1802)—as administering gas at London's Royal Institution to a particularly long-winded (and flatulent!) Member of Parliament, Sir John Coxe Hippisley (1748–1825). Squeezing the bellows (of laughing gas?) next to the pair is the grinning future Sir Humphry Davy. Just over a week after Hannah Humphrey published Gillray's etching, Davy would replace Garnett as the Royal Institution's Lecturer of Chemistry. In contrast to Garnett's complicated and listless diatribes, Davy's animated lectures were so popular that London had to initiate its first one-way street to handle arriving traffic. In contrast, already devastated by the loss of his wife in childbirth on Christmas Day of 1798, the hapless Garnett would die of typhus less than a month after resigning from the Royal Institution. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.