Pharyngeal Function and Breathing Pattern during Partial Neuromuscular Block in the Elderly

Effects on Airway Protection

Anna I. Hårdemark Cedborg, M.D., Eva Sundman, M.D., Ph.D., Katarina Bodén, M.D., Ph.D., Hanne Witt Hedström, M.D., Ph.D., Richard Kuylenstierna, M.D., Ph.D., Olle Ekberg, M.D., Ph.D., Lars I. Eriksson, M.D., Ph.D., F.R.C.A.

ABSTRACT

Background: Intact pharyngeal function and coordination of breathing and swallowing are essential for airway protection and to avoid respiratory complications. Postoperative pulmonary complications caused by residual effects of neuromuscular-blocking agents occur more frequently in the elderly. Moreover, elderly have altered pharyngeal function which is associated with increased risk of aspiration. The purpose of this study was to evaluate effects of partial neuromuscular block on pharyngeal function, coordination of breathing and swallowing, and airway protection in individuals older than 65 yr.

Methods: Pharyngeal function and coordination of breathing and swallowing were assessed by manometry and videoradiography in 17 volunteers, mean age 73.5 yr. After control recordings, rocuronium was administered to obtain steady-state train-of-four ratios of 0.70 and 0.80 followed by spontaneous recovery to greater than 0.90.

Results: Pharyngeal dysfunction increased significantly at train-of-four ratios 0.70 and 0.80 to 67 and 71%, respectively, compared with 37% at control recordings, and swallowing showed a more severe degree of dysfunction during partial neuromuscular block. After recovery to train-of-four ratio of greater than 0.90, pharyngeal dysfunction was not significantly different from the control state. Resting pressure in the upper esophageal sphincter was lower at all levels of partial neuromuscular block compared with control recordings. The authors were unable to demonstrate impaired coordination of breathing and swallowing.

Conclusion: Partial neuromuscular block in healthy elderly individuals causes an increased incidence of pharyngeal dysfunction from 37 to 71%, with impaired ability to protect the airway; however, the authors were unable to detect an effect of partial neuromuscular block on coordination of breathing and swallowing. (ANESTHESIOLOGY 2014; 120:312-25)

RESIDUAL neuromuscular block is frequently seen in the postoperative period,[1,2] and it affects outcome during the first 24 h after surgery.[3] Patients with incomplete reversal of neuromuscular block have an increased risk of hypoxic events in the postanesthesia care unit[4] with a subsequently increased risk of serious adverse events in the postoperative period.[2,5,6] In particular, postoperative pulmonary complications are significantly more common in patients with residual effects of neuromuscular-blocking agents (NMBAs), and the risk of postoperative pulmonary complications is markedly increased among elderly patients, that is, patients older than 60 yr,[5] a steadily growing part of the surgical population worldwide.

It is well known that elderly individuals exhibit an impaired pharyngeal function,[7] seen as an increased frequency of misdirected swallowing and tracheal aspiration.[8–11] Moreover, aging has previously been shown to affect coordination of breathing and swallowing, primarily seen as an increased number of swallows occurring during inspiration,[12] longer periods of apnea during swallowing, and differences in

What We Already Know about This Topic

- Elderly individuals have impaired pharyngeal function. Partial neuromuscular block causes pharyngeal dysfunction even in young volunteers. Little is known about the effects of partial paralysis on pharyngeal function in elderly people.

What This Article Tells Us That Is New

- Incidence of swallowing dysfunction increased more than double during partial neuromuscular block in healthy elderly individuals without impairment of coordination between swallowing and breathing. Reduced upper esophageal sphincter tone did not recover even at the train-of-four ratio of 0.9.

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timing of apnea in relation to pharyngeal swallowing,[11,13–15] resulting in increased risk of aspiration.[11,14,16,17] Thus, elderly can be considered as at-risk patients for impaired airway integrity and aspiration in the surgical setting.

In general, residual effects of NMBAs impair pharyngeal function causing reduced pharyngeal dimensions with airway collapsibility during forced ventilation,[18] pharyngeal muscle weakness, and impaired swallowing that may result in aspiration.[19–21] Pharyngeal dysfunction with misdirected or incomplete swallowing gradually increases at mechanical adductor pollicis train-of-four (TOF) ratios of 0.9–0.6.[19,21] As expected, residual effects of NMBAs are associated with an increased risk of postoperative respiratory complications.[2–4] The current knowledge regarding the effects of partial neuromuscular block on the upper airway and the pharynx is primarily gained from series of studies on young adults.[18–21] Although there are well-known changes in pharyngeal function and coordination of breathing by aging *per se*,[7–11] we lack detailed information on the effects of residual neuromuscular block on pharyngeal function and coordination of breathing and swallowing in the elderly population.

In this study, we hypothesize that partial neuromuscular block in elderly individuals (1) increases the incidence of pharyngeal dysfunction compared with the control state, with subsequent misdirected swallowing and aspiration and (2) that this is associated with an altered coordination between breathing and swallowing compared with the control state.

A novel high-resolution technique with simultaneous recordings of breathing patterns and pharyngeal swallowing events has recently been developed.[22–24] By using this setting, we investigated elderly volunteers to gain further knowledge about the impact of residual neuromuscular block on pharyngeal function and breathing patterns.

Materials and Methods

Ethical Approval and Study Population

The study conforms to the standards of the Declaration of Helsinki and was approved by the Regional Ethics Committee on Human Research at the Karolinska Institutet, Stockholm, Sweden. We included 17 elderly volunteers, older than 65 yr of age and without history of diabetes mellitus, dysphagia, gastroesophageal reflux disease, or surgery to the pharynx, esophagus, or larynx, after written informed consent. None used medication interfering with neuromuscular function or breathing. Demographical characteristics are presented in table 1. In addition, a control group of six elderly volunteers (mean age, 71.3 yr [70–73], three women and three men) were included to investigate the stability of recordings over time.

Respiration

A face mask with perforations for catheters and transducers was fixed over the nose and mouth and connected to a breathing circuit (dead space, 90 ml) with a fresh gas flow rate of 12 l/min. Oral and nasal airflow was recorded as previously described[24] with an airflow discriminator (ASF1430, CMOSens®; Sensirion AG, Staefa, Switzerland) that determined beginning and end of inspiratory and expiratory airflow and apnea. Durations (ms) of inspiration, expiration, and apnea were measured and related in time to pharyngeal swallowing events. In addition, a traditional nasal pressure transducer (RespSponse; SynMed, Stockholm, Sweden) was inserted into one nostril and used for visual comparisons of respiratory phases. As previously described,[24] we simultaneously recorded respiration and swallowing to analyze respiratory-phase patterns, that is, to determine during which phase of respiration the swallowing maneuver occurred. Four respiratory-phase patterns have been described,[11,22–24] that is, the most common pattern E-E (inspiration-expiration-swallow apnea-expiration), I-E (inspiration-swallow apnea-expiration), E-I (inspiration-expiration-swallow apnea-inspiration), and finally the very rare I-I (inspiration-swallow apnea-inspiration; fig. 1).

Swallowing and Pharyngeal Function—Videoradiography and Pharyngeal Manometry

A manometry catheter with four solid-state pressure transducers 2 cm apart was introduced through one nostril and advanced so that the most distal transducer was placed in the upper esophageal sphincter (UES).[19,21–24] Correct positioning of catheter was repeatedly confirmed by using intermittent fluoroscopy. Pharyngeal manometry and videoradiography (fluoroscopy) were recorded simultaneously and superimposed during swallowing of contrast medium, as previously described.[22] Three contrast-medium swallows were used to assess signs of pharyngeal dysfunction defined as three categories (1) premature bolus leakage from the mouth to the pharynx and/or (2) penetration of contrast medium into the laryngeal vestibule or the trachea and/or (3) retention of contrast medium in the pharynx after completion of swallowing. In addition, each swallow was analyzed in-depth and scored for pharyngeal dysfunction by using three different methods: (1) degree of pharyngeal dysfunction, adding the number of signs (0–3) of pharyngeal dysfunction category A to C (see above) found in each of the three swallows. The individual sum (0–9) was thereafter divided by the maximal outcome (*i.e.*, 9), yielding the term degree of pharyngeal dysfunction (%); (2) risk of aspiration by using the penetration aspiration scale (PAS)[25]; and (3) efficiency of bolus clearance by using

Table 1. Demographics of the 17 Elderly Volunteers

Age, yr	73.5 ± 4.6	68–85
Weight, kg	72 ± 9	55–91
Height, cm	172 ± 8	155–180
BMI	24.6 ± 2.7	19.0–28.4
Men, n	10	
Women, n	7	

Data presented as mean ± SD and range.
BMI = body mass index; n = numbers.

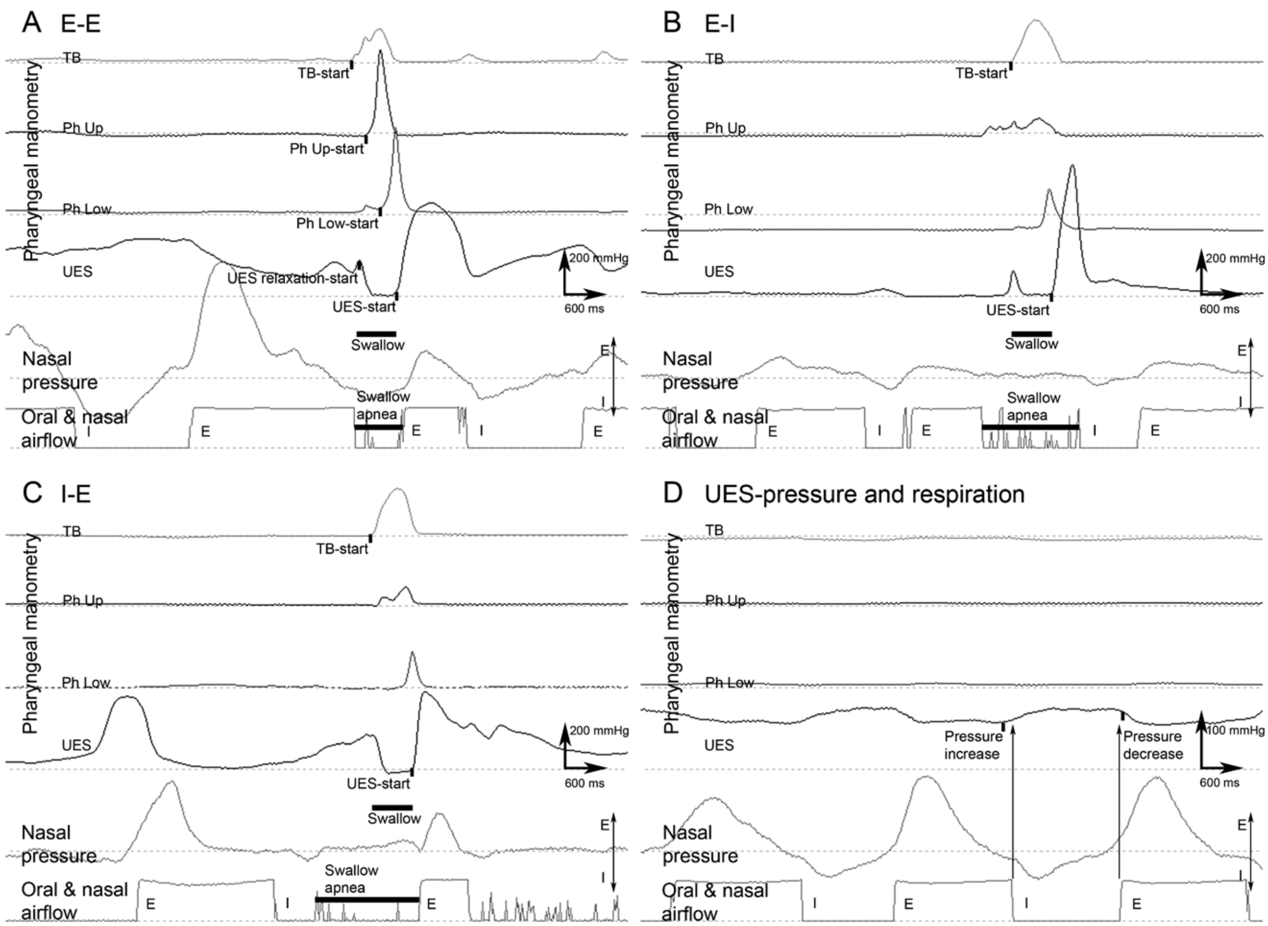

Fig. 1. (*A–C*) Original recordings of simultaneous pharyngeal manometry, nasal pressure, and oral and nasal airflow during spontaneous saliva swallows with the respiratory-phase patterns inspiration-expiration-swallow apnea-expiration (E-E) (*A*), inspiration-expiration-swallow apnea-inspiration (E-I) (*B*), and inspiration-swallow apnea-expiration (I-E) (*C*). Respiratory-phase patterns E-E and E-I were recorded during control conditions, whereas I-E was recorded at train-of-four (TOF) ratio 0.70. Manometry recordings made at tongue base (TB), upper or lower pharyngeal transducer (Ph Up, Ph Low), and upper esophageal sphincter (UES) levels. Swallow indicates duration of pharyngeal swallowing. Start of pressure increase at the TB-start, upper and lower pharyngeal transducer level (Ph Up-start, Ph Low-start), UES (UES-start), and start of relaxation of the UES (UES relaxation-start) is indicated. Swallow apnea was detected as an oscillating signal (zero airflow) from the gas flow discriminator (Oral and nasal airflow). (*D*) UES pressure variations with respiration recorded during control conditions. Start of inspiration (I) and start of expiration (E) are marked with *arrows* (↑). In pharyngeal manometry, the *dotted baseline* represents pressure = 0 mmHg.

the valleculae residue scale (VRS)[25] and the pyriform sinus residue scale (PRS),[25] all three being validated scales. The start of pharyngeal swallowing was defined as the beginning of pressure increase at the tongue base (TB-start), whereas the end was defined as the beginning of UES contraction (UES-start)[22–24] (fig. 1A). All events regarding timing of swallow apnea and pharyngeal manometry were referenced in time to TB-start (TB-start = 0 ms). Manometry recordings were made at the TB, at two levels of the pharyngeal constrictor muscles (at an upper level [Ph Up] and a lower level [Ph Low]) and in the UES. Maximum contraction pressure (amplitude, mmHg) was analyzed at three levels (TB, Ph Low, and UES). Contraction rate (slope, mmHg/s) and duration of contraction (ms) were analyzed at two levels (TB and Ph Low). Coordination between pharyngeal muscles (coordination) was measured as the time between the start of pressure increase in the lower part of the pharyngeal constrictor (Ph Low) and the start of UES relaxation (UES relaxation-start). In addition, the mean UES pressure during 10 s without swallowing as well as the UES pressure variation during inspiration and expiration at rest was measured (mmHg).[23] By using videoradiography, the time point when the head of the bolus passed the anterior faucial arches was determined and compared with (1) the start of the hyoid bone forward movement (initiation of the pharyngeal phase of swallowing [ms]) and (2) when the tail of the bolus reached below the UES (bolus transit time [ms]).[21] Videoradiographic images were interpreted by an experienced radiologist. To minimize the radiation dose to subjects, spontaneous swallows of saliva were recorded by pharyngeal manometry without videoradiography. All swallowing maneuvers of contrast medium and three spontaneous saliva swallows (for selection criteria, see Statistical Analysis), with the respiratory-phase pattern E-E were analyzed regarding timing of pharyngeal swallowing events and swallow apnea (all measured in relation to TB-start [ms]), durations of inspirations and expirations before and after swallow apnea (ms), swallow apnea duration (SAD) (ms), UES maximum contraction pressure (mmHg), and coordination (ms). Preswallow apnea was defined as the time from onset of swallow apnea to onset of pharyngeal swallowing (TB-start) (ms) and postswallow apnea as the time from the end of pharyngeal swallowing (UES-start) to the end of swallow apnea (ms).

Neuromuscular Block and Monitoring

Neuromuscular transmission was assessed conforming to international guidelines for neuromuscular research[26] by isometric mechanomyography of the adductor pollicis with the use of a Biometer Myograph 2000 neuromuscular transmission analyzer (Organon Teknika, Boxtel, The Netherlands). Before start of experiments, a preload of 0.20–0.35 kg was applied to the thumb, and supramaximal ulnar nerve stimulation at the wrist was delivered by using surface electrodes connected to a Myotest nerve stimulator (Biometer, Odense Denmark). The electrical stimulus applied for supramaximal ulnar nerve stimulation was set at 15–20% above what was necessary for a maximal response.[26] The evoked mechanical adductor pollicis twitch response was allowed to stabilize during continuous ulnar nerve stimulation (1 Hz for 15–20 min). After a stable twitch response had been obtained, ulnar nerve TOF stimulation (0.3 ms^2 impulses at 2 Hz for 1.5 s every 12 s) was initiated and calibrated. During the experimental period, the peripheral hand temperature was monitored (Datex-Ohmeda Cardiocap®/5; GE Healthcare, Madison, WI) and kept above 32.0°C by intermittently using a warming blanket. Room temperature was kept at 23°C (range, 22°–24°C). An intravenous rocuronium infusion was started at 35–45 mg/h, thereafter adjusted to 0.28 ± 0.10 mg kg^{-1} h^{-1} and 0.19 ± 0.09 mg kg^{-1} h^{-1}, yielding TOF ratios of 0.70 ± 0.01 and 0.80 ± 0.01, respectively. To ensure steady state, TOF ratios had to be stable for a minimum of 5 min before recordings began. The mean time to reach TOF ratio 0.70 and TOF ratio 0.80 was 21 ± 4 min (range, 16–30 min) and 6 ± 4 min (range, 1–13 min), respectively. The average (mean) total amount of rocuronium given to volunteers was 0.3 ± 0.1 mg/kg (range, 0.1–0.5 mg/kg) during a time period of 54 ± 11 min (range, 40–79 min). After termination of the rocuronium administration (*i.e.*, at steady-state TOF ratio 0.80), the mean time to reach TOF ratio greater than 0.90 (0.96 ± 0.03) was 5 ± 2 min (range, 1–7 min).

Study Protocol

Volunteers were allowed solid food until 6 h and liquids until 2 h before entering the study. An intravenous cannula was placed in a cubital vein, and a continuous infusion of normal saline was administered at a rate of 50 ml/h. Volunteers were then examined in the left lateral position with an 8 degree head up tilt. After initial control recordings, rocuronium (Esmeron®; Merck & Co. Inc., Whitehouse Station, NJ) (50 mg dissolved in 100 ml normal saline, *i.e.*, 0.5 mg/ml) was administered as a continuous intravenous infusion by using a motor syringe (Terumo, Tokyo, Japan) that was adjusted to obtain steady-state TOF ratios (T4/T1) of 0.70 and 0.80 followed by spontaneous recovery to greater than 0.90 (fig. 2). At each of these four study conditions, breathing and spontaneous swallows of saliva were recorded during a 10-min period while volunteers were resting (fig. 2). This was followed by recordings of three bolus swallows of 10 ml water-soluble contrast medium (Omnipaque 240 mg/ml; Nycomed Imaging, Oslo, Norway) (fig. 2) with a temperature of 22°–24°C. Subjects were also asked to estimate their level of sedation on a visual analogue scale (VAS, VAS-sedation), where 0 was maximal sedation, just falling asleep, and 10 was no sedation. Coughing associated with swallowing of contrast medium was recorded. Respiratory rate (breaths/min) and spontaneous swallowing frequency (swallows/min) were calculated. Vital parameters (heart rate, noninvasive blood pressure, end-tidal carbon dioxide, and peripheral oxygen saturation) were monitored continuously (Datex-Ohmeda Cardiocap®/5; GE Healthcare, Madison, WI). Recordings at each of the four study conditions lasted for approximately 15 min. The total time the volunteers were examined was 97 ± 12 min (range, 70–118 min).

Control Group

In the control group (n = 6), the stability of recording was assessed to rule out an effect of elapsed time on pharyngeal dysfunction and UES pressure at rest. Assessments were made at four occasions with the use of pharyngeal manometry and videoradiography as described above (see Materials and Methods, Respiration, and Swallowing and Pharyngeal Function), that is, at 0 (baseline), 25, 50, and 75 min.

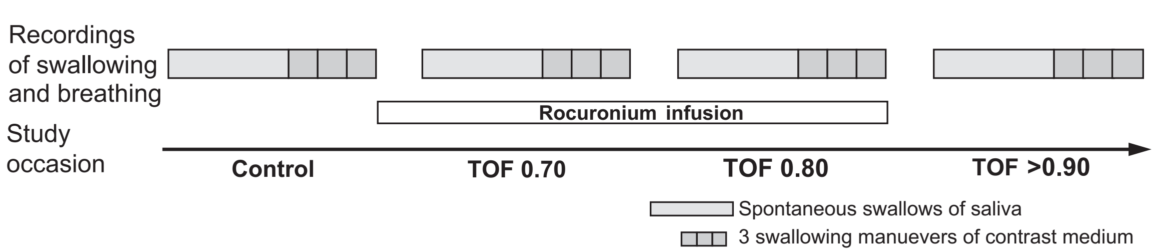

Fig. 2. Schematic presentation of study protocol. Recordings at control (control) and during three levels of partial neuromuscular block (train-of-four [TOF] ratios 0.70, 0.80, and >0.90).

Corresponding percentage of swallows with pharyngeal dysfunction was 44, 27, 50, and 39% (P = 0.42), whereas UES mean pressure at rest (mmHg) was 64 ± 13, 68 ± 27, 79 ± 37, and 84 ± 32 at 0, 25, 50, and 75 min (P = 0.51), confirming the stability of the method over time.

Statistical Analysis

Mean UES pressure at rest was measured before and after the swallowing maneuvers of contrast medium, and a mean value was calculated for each volunteer at each of the four levels of partial neuromuscular block (control, TOF ratios 0.70, 0.80, and >0.90). For all other parameters derived from manometry, videoradiography, and airflow (durations [ms], intervals [ms], and timing of events from TB-start = 0 [ms], pressures [mmHg], contraction rates [mmHg/s], PAS, VRS, and PRS), a mean value based on three measurements from three separate swallows or breaths was calculated for each volunteer and at each of the four levels of partial neuromuscular block (control, TOF ratios 0.70, 0.80, and >0.90). For in-depth analysis of coordination of breathing and swallowing, swallows with the respiratory-phase pattern E-E were chosen, because the number of recorded non-E-E swallows was too small to allow statistical analysis. When studying spontaneous swallows or breaths at rest, measurements were made in the first E-E swallow occurring closest to the start, mid, and end period of the recording, to avoid selection bias. For all statistical analysis, Statistica 10 (Statsoft® Inc., Tulsa, OK) was used when not otherwise stated. For data suitable for parametric analysis, ANOVA repeated measures (one or two within factors) was used. Planned comparisons comparing control to measurements at TOF ratios 0.70, 0.80, and greater than 0.90 and between spontaneous swallows of saliva and swallows of contrast medium were made, respectively. Results are presented as mean ± SD of the mean (SD) or the 95% CI. For data included in degree of pharyngeal dysfunction, PAS, VRS, PRS, and VAS-sedation, planned comparisons were made using Wilcoxon test. Percentage of swallows with pharyngeal dysfunction was analyzed using ANOVA after rank transformation. Results are presented as median values with upper and lower quartile and range. Respiratory-phase patterns were analyzed for all swallows, that is, spontaneous swallows of saliva and swallows of contrast medium, using generalized linear models (PROC GENMOD, logistic regression, repeated measures with binary data) using SAS® 9.2, maintenance 2, (SAS® Institute Inc., Cary, NC) because this procedure can handle complex data structures and allows for variations in the total number of swallows at each of the four levels of partial neuromuscular block (control, TOF ratios 0.70, 0.80, and >0.90) (spontaneous swallows of saliva occurred with varying frequency). Analysis of effects of sex was, for data suitable for parametric analysis, made using ANOVA repeated measures with a categorical predictor and for data analyzed with nonparametric methods using Mann–Whitney U test. To investigate factors that could be associated with pharyngeal dysfunction, degree of pharyngeal dysfunction at TOF ratio 0.70 was analyzed for effects of sex and respiratory-phase patterns (*i.e.*, presence of non–E-E phase patterns) using Mann–Whitney U test. Family-wise Bonferroni corrections for multiple comparisons were made. Exact unadjusted P values are reported. P values less than 0.05 were considered significant.

Results

Swallowing and Pharyngeal Dysfunction

A total of 669 swallowing maneuvers were analyzed, 203 swallows of contrast medium and 466 spontaneous swallows of saliva. Pharyngeal dysfunction was analyzed by using videoradiography in the contrast-medium swallows. In control recordings, 37% of swallows showed at least one of the criteria for pharyngeal dysfunction. This increased to 67 and 71% during partial neuromuscular block with TOF ratios 0.70 and 0.80, respectively (table 2). After recovery to a TOF ratio of greater than 90%, there was no difference from the control state (table 2). Because pharyngeal dysfunction was frequently found in the control state, and swallows with more than one of the signs of dysfunction were common during partial neuromuscular block, we further explored the severity of pharyngeal dysfunction (for definition see Materials and Methods). Degree of pharyngeal dysfunction (fig. 3) increased from a median of 11% (0–77%), during control conditions, to 33% (0–77%; P = 0.005) and 33% (11–77%; P = 0.013) at TOF ratios 0.70 and 0.80, respectively (fig. 3A). Again, after recovery to TOF ratio of greater than 0.90, the degree of pharyngeal dysfunction was not significantly different from the control state (0–56%; P = 0.31) (fig. 3A). Videoradiographical analysis revealed that penetration of contrast medium occurred to, or to a level immediately above the vocal cords (laryngeal penetration). However, contrast medium was not detected below the vocal cords (aspiration) in any of the swallowing maneuvers. Risk of aspiration assessed using PAS and efficiency of bolus clearance using VRS and PRS revealed an increased VRS score at TOF ratio 0.70 compared with the control state (table 2). However, at TOF ratios 0.80 and greater than 0.90, scores were not different compared with control (table 2). Comparing men and women, there were no detectable differences in the incidence of pharyngeal dysfunction or degree of pharyngeal dysfunction during partial neuromuscular block.

Coordination of Breathing and Swallowing

Respiratory-phase patterns were not affected by partial neuromuscular block (P = 0.34) (fig. 3B). The majority of swallows occurred during expiration with expiratory airflow present both before and after swallow apnea (E-E) (fig. 1A). Two other patterns were detected, I-E, where swallowing occurs immediately after inspiration and is followed by expiratory airflow, and E-I, where swallowing is followed by inspiratory airflow (fig. 1, B–C). None of the swallowing maneuvers occurred during the inspiratory phase (I-I). Notably, I-E and E-I swallows were not associated with a

Table 2. Pharyngeal Dysfunction, Penetration–Aspiration and Bolus Clearance during Partial Neuromuscular Block

		Control	TOF 0.70	TOF 0.80	TOF >0.90
Percentage of swallows with pharyngeal dysfunction	%	37	67*	71*	45
	P		0.014	0.009	0.44
Swallows with premature leakage of bolus	n	12	18	23	14
Swallows with penetration of bolus to laryngeal inlet	n	10	16	15	7
Swallows with retention of bolus after swallow	n	4	18	16	10
Penetration aspiration scale† (1–8)	Median	1.0	1.3	1.3	1.0
	P		0.033	0.09	0.72
	Q1 to Q3	1–1.3	1–2.0	1–2.0	1–1.0
	Range	1–4.3	1–4.7	1–4.7	1–3.3
Valleculae residue scale‡ (1–3)	Median	1.0	1.3*	1.0	1.0
	P		0.012	0.028	0.18
	Q1 to Q3	1–1.0	1–1.7	1–1.7	1–1.3
	Range	1–1.7	1–2.0	1–2.0	1–1.7
Pyriform sinus residue scale‡ (1–3)	Median	1.0	1.0	1.0	1.0
	P		0.043	0.59	0.71
	Q1 to Q3	1–1.0	1–1.7	1–1.0	1–1.0
	Range	1–1.7	1–2.0	1–2.0	1–1.7
Total swallowing maneuvers of contrast medium	n	51	51	51	51

* *P* < 0.05 after Bonferroni correction. † Penetration aspiration scale (1–8); risk of aspiration rated such as: *No risk*, 1 = no airway invasion; 2 = bolus enters into airway with clearing; *Risk of Aspiration*, 3 = bolus enters into airway without clearing; 4 = bolus contacts vocal cords with airway clearing; 5 = bolus contacts vocal cords without airway clearing; *Positive Aspiration*, 6 = bolus enters trachea and is cleared into larynx or out of airway; 7 = bolus enters trachea and is not cleared despite attempts; 8 = bolus enters trachea and no attempt is made to clear. ‡ Valleculae and Pyriform sinus residue scale (1–3); Bolus clearance rated, 1 = no residual to mild bolus retention; 2 = moderate residual with up to half the recess filled with material postswallow; 3 = severe residual with more than half the recess filled with material postswallow.

n = numbers; *P* = exact *P* value *vs.* control; Q1 to Q3 = lower and upper quartile; TOF = train-of-four ratio.

higher degree of pharyngeal dysfunction compared with E-E swallows. There were no differences in respiratory-phase patterns or coordination of breathing and swallowing when comparing men and women.

When further analyzing E-E swallows, partial neuromuscular block had no effect on duration of inspiration before swallowing, expiration before swallowing, preswallow apnea (fig. 4), pharyngeal swallowing (fig. 4), postswallow apnea, or expiration after swallowing. Moreover, partial neuromuscular block had no effect on SAD being 1,280 ± 789, 1,128 ± 267, 1,571 ± 893, and 1,379 ± 513 ms at control, TOF ratios 0.70, 0.80, and greater than 0.90, respectively (*P* = 0.08). Hence, we could not detect an effect by partial neuromuscular block on coordination of breathing and swallowing.

Mechanical Properties and Timing of Pharyngeal Swallowing and Swallow Apnea

In swallowing maneuvers of both contrast medium and saliva occurring within the respiratory-phase pattern E-E, partial neuromuscular block had no effect on the time course of the pharyngeal muscle contraction wave (fig. 4). Neither were there any effects of partial neuromuscular block on the start or end of swallow apnea in relation to pharyngeal swallowing (fig. 4). The duration of the pharyngeal phase of swallowing (TB-start to UES-start) was shorter in men compared with women (*P* = 0.013, ANOVA), previously explained as anatomical differences[8]; however, this was not affected by partial neuromuscular block. There were no other differences regarding the time course of the pharyngeal muscle contraction wave or swallow apnea in relation to pharyngeal swallowing when comparing men and women.

When further analyzing pharyngeal manometric pressures in swallowing maneuvers of contrast medium, partial neuromuscular block had no significant effect on maximum contraction pressure, contraction rate, or contraction duration, either at the level of the base of the tongue (TB) or at the lower pharyngeal constrictor muscle (Ph Low) (table 3). There was no effect of partial neuromuscular block on the coordination between UES relaxation and pharyngeal constrictor muscle activity, neither in contrast-medium swallows nor in spontaneous swallows of saliva (table 3).

Partial neuromuscular block had no significant effect on initiation of the pharyngeal phase of swallowing, bolus transit time, or the time interval between when the bolus was first seen in the mouth and onset of pharyngeal swallowing (TB-start) (table 3). In five volunteers and 8 of 51 swallows during control recordings, we recorded a bolus present in the mouth without initiation of pharyngeal swallowing, yet pharyngeal contractions occurred without contrast medium being propelled. This was later followed by subsequent contractions, that is, the actual swallowing maneuver, where the bolus was transported into the esophagus. In this subset of volunteers, this pattern was not changed by partial neuromuscular block. Finally, there were no differences in maximum contraction pressures, contraction rate, contraction duration, coordination, initiation, bolus transit time, or bolus in mouth without initiating pharyngeal swallowing when comparing men to women.

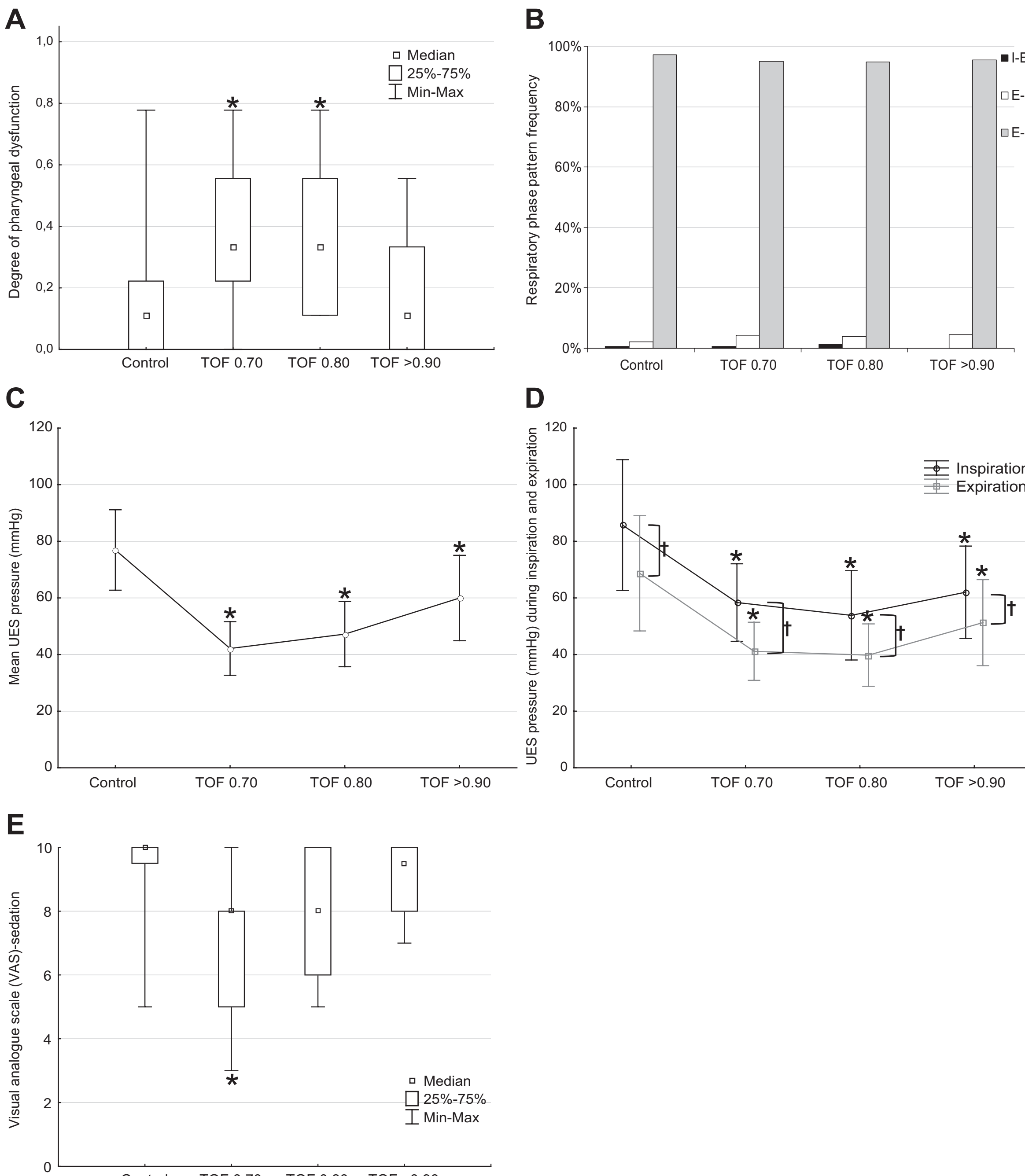

Fig. 3. (*A*) Degree of pharyngeal dysfunction at control (control) and during three levels of partial neuromuscular block (train-of-four [TOF] ratios 0.70, 0.80, and >0.90). Severity of pharyngeal dysfunction increased significantly during partial neuromuscular block in the elderly and an increased number of swallows showed multiple abnormalities. **P* < 0.05 *versus* control. (*B*) Frequency (%) of respiratory-phase patterns (inspiration-expiration-swallow apnea-expiration [E-E]; inspiration-expiration-swallow apnea-inspiration [E-I]; inspiration-swallow apnea-expiration [I-E]) during swallowing at control (control) and during partial neuromuscular block (TOF ratios 0.70, 0.80, and >0.90). The coordination of breathing and swallowing was not affected by partial neuromuscular block. (*C*) Mean upper esophageal sphincter (UES) pressure at control and during partial neuromuscular block (TOF ratios 0.70, 0.80, and >0.90). The UES pressure (mmHg) was measured at rest for 10 s without swallowing and decreased during partial neuromuscular block. *Vertical bars* denote 95% CI. **P* < 0.05 *versus* control. (*D*) Variation in UES pressure (mmHg) with respiration, at control and during partial neuromuscular block (TOF ratios 0.70, 0.80, and >0.90). Partial neuromuscular block lowered UES pressures both during inspiration and expiration, but the difference in pressure during inspiration and expiration was preserved. *Vertical bars* denote 95% CI. **P* < 0.05 *versus* control. †*P* < 0.05 inspiration *versus* expiration. (*E*) Self-estimated sedation score at control (control) and during partial neuromuscular block (TOF ratios 0.70, 0.80, and >0.90). On a visual analogue scale (VAS) where 0 equals maximal sedation (*i.e.*, just falling asleep) and 10 equals no sedation, the volunteers scored themselves lower (less vigilant) during partial neuromuscular block. **P* < 0.05 *versus* control.

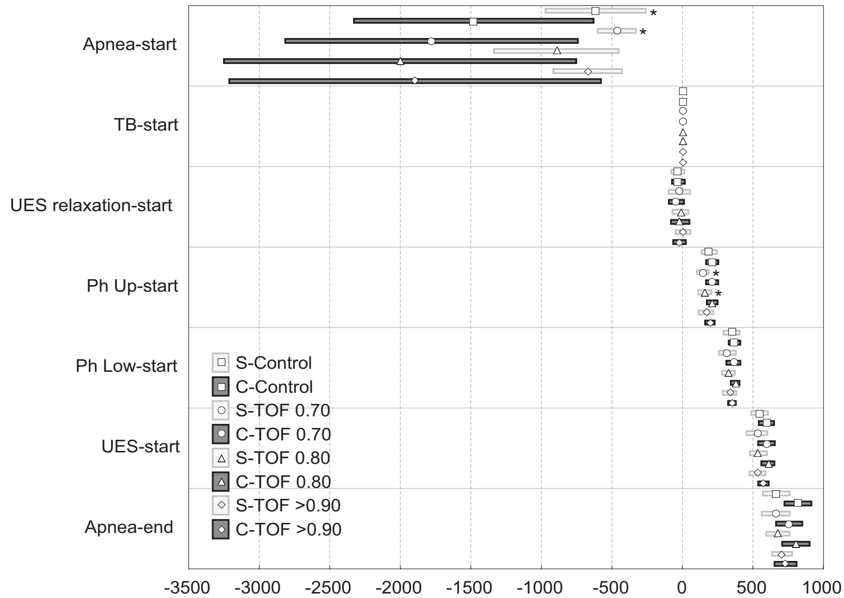

Fig. 4. Pharyngeal swallowing and swallow apnea in spontaneous swallows of saliva (S) and swallowing maneuvers of contrast medium (C), with the respiratory-phase pattern inspiration-expiration-swallow apnea-expiration (E-E), at control (control) and during three levels of partial neuromuscular block (train of four [TOF] ratios 0.70, 0.80, and >0.90). The start of pharyngeal swallowing was defined as the onset of pressure increase at the tongue base (TB-start) and all pharyngeal manometry events as well as start and end of swallow apnea were referenced in time (ms) to TB-start = 0. Start of relaxation of the upper esophageal sphincter (UES) (UES relaxation-start). Onset of pressure increase in the upper and lower pharyngeal manometry transducer (Ph Up-start and Ph Low-start) and the UES (UES-start). Start of swallow apnea (Apnea-start) and end of swallow apnea (Apnea-end). Mean (ms) ± 95% CI. *$P < 0.05$ *versus* swallowing maneuvers of contrast medium.

UES

Resting UES pressures were significantly decreased at all levels of partial neuromuscular block (TOF 0.70, $P < 0.001$; 0.80, $P < 0.001$; and >0.90, $P = 0.007$) compared with control recordings (fig. 3C). Inspiratory UES pressures were significantly higher than expiratory UES pressures (figs. 1D and 3D). The timing of UES pressure changes in relation to onsets of inspiration and expiration, where an increase in UES pressure occurs before start of inspiration and a decrease in UES pressure is seen after expiration, are shown in figure 1D. This coordination between UES pressure changes and breathing was not affected by partial neuromuscular block; however, both the inspiratory and expiratory UES pressures were lower at all levels of partial neuromuscular block compared with control recordings ($P < 0.001$; fig. 3D). Partial neuromuscular block had no further effect on the maximum contraction pressure in the UES after swallowing (table 3). Finally, we were unable to detect any differences in UES pressures or coordination with breathing when comparing men and women.

Cough

During control recordings, three volunteers coughed when swallowing one of the three boluses of contrast medium. At TOF ratios 0.70 and 0.80, one volunteer coughed and at TOF ratio greater than 0.90, two volunteers coughed when swallowing one of the three boluses of contrast medium. The total number of coughs was too small to allow statistical analysis.

Sedation Scoring by VAS and Subjective Symptoms of Neuromuscular Block

Visual analogue scale scoring decreased during partial neuromuscular block, that is, most volunteers scored themselves more sedated at TOF ratio 0.70 as compared with the control state (TOF ratios 0.70, $P < 0.001$; 0.80, $P = 0.041$; and >0.90, $P = 0.13$; fig. 3E). Moreover, there was a significant difference in VAS-sedation between men and women at TOF ratio 0.70. Men felt more affected and scored themselves lower (median, 6.3; range, 3.0–8.5) than women (median, 8.0; range, 5.0–10.0; $P = 0.033$).

At TOF ratio 0.70, volunteers spontaneously described symptoms such as blurred vision, diplopia, dysarthria, subjective difficulty to swallow, relaxed facial muscles, and calmness. None reported distress or discomfort and none had trouble breathing. All volunteers completed the study at all levels of partial neuromuscular block and mechanomyography was well tolerated. Vital parameters including respiratory rate and spontaneous swallow frequency (0.8 ± 0.5, 0.7 ± 0.3, 0.6 ± 0.4, and 0.6 ± 0.3 swallows per minute at control, TOF ratios 0.70, 0.80, and greater than 0.90, respectively [$P = 0.12$]) were unchanged throughout the study.

Bolus Type

When comparing swallowing maneuvers of contrast medium to spontaneous swallows of saliva, coordination was longer for swallows of contrast medium at TOF ratio 0.70 (table 3). The maximum contraction pressure in the UES

Table 3. Mechanical Properties and Timing of Pharyngeal Swallowing during Partial Neuromuscular Block

		Bolus	Control	TOF 0.70	TOF 0.80	TOF >0.90	*P* Value, NMBA
Pharyngeal Manometry							
TB max. contr.	mmHg	C	247 ± 211	207 ± 101	316 ± 333	313 ± 331	0.11
TB contr. Rate	mmHg/s	C	944 ± 648	907 ± 791	1,240 ± 1,196	1,207 ± 1,029	0.12
TB contr. dur.	ms	C	676 ± 163	650 ± 144	695 ± 121	678 ± 116	0.51
Ph Low max. contr.	mmHg	C	315 ± 103	333 ± 135	303 ± 126	301 ± 136	0.38
Ph Low contr. Rate	mmHg/s	C	1,448 ± 538	1,522 ± 670	1,338 ± 595	1,426 ± 716	0.47
Ph Low contr. dur.	ms	C	553 ± 125	550 ± 116	537 ± 121	522 ± 97	0.57
Coordination	ms	C	−398 ± 64	−403 ± 83	−390 ± 121	−371 ± 75	0.63
Coordination	ms	S	−381 ± 98	−341 ± 92*	−340 ± 98	−331 ± 75	0.14
	P, Bolus	S *vs.*C	0.38	0.007	0.17	0.016	
UES max. contr.	mmHg	C	371 ± 126	330 ± 99	344 ± 123	370 ± 137	0.15
UES max. contr.	mmHg	S	274 ± 109*	268 ± 140	281 ± 134*	285 ± 114*	0.90
	P, Bolus	S *vs.*C	0.004	0.017	0.010	<0.001	
Videoradiography							
Initiation	ms	C	137 ± 124	177 ± 277	159 ± 167	146 ± 120	0.89
Bolus transit time	ms	C	914 ± 166	976 ± 334	984 ± 206	941 ± 197	0.77
Bolus in mouth	s	C	5.6 ± 4.5	3.9 ± 2.6	4.4 ± 4.2	5.2 ± 7.4	0.18

N = 17 elderly volunteers. Data presented as mean ± SD; *P* value, NMBA, *P* value (ANOVA); *P*, Bolus, exact *P* value *vs.* swallowing maneuvers of contrast medium (ANOVA, planned comparisons). Measurements of pharyngeal manometry are illustrated in figure 6.

* $P < 0.05$ after Bonferroni correction.

Bolus = bolus type; Bolus in mouth, without initiating pharyngeal swallowing = the interval between the times at which the bolus of contrast medium was first seen in the mouth and onset of pharyngeal swallowing, *i.e.*, start of pressure increase at the level of the TB (TB-start); Bolus transit time (pharyngeal) = the interval between the times at which the bolus head passed the anterior faucial arches and the tail of the bolus passed the UES; C = swallowing maneuvers of contrast medium; contr. dur. = contraction duration; contr. rate = contraction rate; coordination = measured as the time between the start of pressure increase at the lower part of the pharyngeal constrictor (Ph low-start) and the start of UES relaxation (UES relaxation-start); Initiation of the pharyngeal phase of swallowing = the interval between the times at which the head of the bolus passed the anterior faucial arches and the hyoid bone started to move forward; max. contr. = maximum contraction pressure; NMBA = neuromuscular-blocking agent; Ph Low = lower pharyngeal manometry transducer; TB = tongue base; TOF = train-of-four ratio; S = spontaneous swallows of saliva; UES = upper esophageal sphincter.

after swallowing was significantly higher in contrast-medium swallows compared with spontaneous saliva swallows, yet this difference was unaffected by partial neuromuscular block (table 3). Moreover, duration of preswallow apnea was longer in swallows of contrast medium at control recordings ($P = 0.008$) and at TOF ratio 0.70 ($P = 0.011$; fig. 4). Also, the time differences from TB-start to Ph Up-start at TOF ratio 0.70 ($P < 0.001$) and TOF ratio 0.80 ($P = 0.006$) were longer in swallowing maneuvers of contrast medium (fig. 4).

Discussion

This study is to our knowledge the first to document the effects of partial neuromuscular block on airway protection and the coordination of breathing and swallowing in healthy elderly individuals. It demonstrates a profound negative impact on airway integrity, increasing the incidence of pharyngeal dysfunction from 37% in the control state to 71% during partial neuromuscular block. However, we were unable to detect an effect of partial neuromuscular block on the coordination of breathing and swallowing.

Oropharyngeal dysphagia is an important etiologic factor for pneumonia in elderly individuals,[27,28] and age *per se* is a risk factor for impaired pharyngeal function, abnormal swallowing, and aspiration.[8–11,29–31] It is thus not surprising that we found a high incidence of pharyngeal dysfunction in the control recordings. We know from studies in young adults that partial neuromuscular block increases the incidence of pharyngeal dysfunction. In the elderly, this extended to a majority of swallows, despite limited depth of block. This cannot be explained by age-dependent differences in rocuronium potency.[32] Rather, it is likely that age-induced decline in pharyngeal function reduces the margins of safety during swallowing and so accentuates the effects of NMBAs. Hence, elderly are prone to adverse pharyngeal effects of residual neuromuscular block. Not studied in this investigation, these effects may remain longer because of the decreased elimination rate of rocuronium in elderly,[32] further increasing the risk for pulmonary complications.[3]

To in detail describe the severity of the pharyngeal dysfunction in this population with a markedly high incidence of misdirected swallowing, we graded the degree of dysfunction by analyzing how many of the three signs of dysfunction were present in each swallow. Penetration of contrast medium into the laryngeal vestibule may obviously lead to aspiration. However, insufficient oral bolus control with premature leakage into the pharynx without initiating pharyngeal swallowing, or pharyngeal bolus residues after swallowing, may also lead to aspiration. Acknowledging this, we analyzed the degree of pharyngeal dysfunction taking all three aspects equally into consideration. During partial neuromuscular block, the degree of pharyngeal dysfunction increased three-fold, and more swallows showed multiple signs of dysfunction.

Table 4. Pharyngeal Function and Coordination of Breathing and Swallowing at the Resting Control State

	Elderly	Young
Pharyngeal Function	**N = 17**	**N = 18**
Swallows of contrast medium, n	51	88†
Incidence of pharyngeal dysfunction, %	37	6
Swallows with premature leakage of bolus, n	12	1
Swallows with penetration of bolus to laryngeal inlet, n	10	4
Swallows with retention of bolus after swallow, n	4	0
UES mean pressure at rest, mmHg	77 ± 28	79 ± 26
Coordination*, ms	−398 ± 64	−465 ± 151
Coordination of Breathing and Swallowing	**N = 17**	**N = 32**
Spontaneous swallows of saliva, n	139	515§
Respiratory-phase patterns, %		
E-E	97.1	97.5
I-E	0.0	0.0
E-I	2.9	2.5
I-I	0.0	0.0
SAD, ms	1,280 ± 789	1,099 ± 411
Duration of pre-swallow apnea, ms	615 ± 691	360 ± 351
Duration of post-swallow apnea, ms	118 ± 115	137 ± 87
Swallows of contrast medium, n	51	93‡
Respiratory-phase patterns, %		
E-E	98.0	97.8
I-E	2.0	1.1
E-I	0.0	1.1
I-I	0.0	0.0
SAD, ms	1,932 ± 1,040	2,237 ± 1,283
Duration of pre-swallow apnea, ms	1,479 ± 1,652	1,292 ± 992
Duration of post-swallow apnea, ms	208 ± 177	399 ± 536

Data from current study on elderly and previous studies on young volunteers. Data presented as mean ± SD. Respiratory-phase patterns (frequency, %).
* Coordination, measured as the time between the start of pressure increase at the lower part of the pharyngeal constrictor (Ph Low-start) and the start of UES relaxation (UES relaxation-start). † Sundman *et al.*[21] ‡ Boden *et al.*[22] § Hårdemark Cedborg *et al.*[23]
E-E = inspiration-expiration-swallow apnea-expiration; E-I = inspiration-expiration-swallow apnea-inspiration; I-E = inspiration-swallow apnea-expiration; I-I = inspiration-swallow apnea-inspiration; N = number of volunteers; n = number of swallows; SAD = swallow apnea duration; UES = upper esophageal sphincter.

In control recordings, in-depth analysis of risk of aspiration using PAS, and efficiency of bolus clearance using VRS and PRS, revealed scores in line with previous results in healthy elderly.[25] Partial neuromuscular block at TOF ratio 0.70 decreased efficiency of bolus clearance, leaving significant bolus residues at the level of the valleculae. However, at TOF ratio 0.80, there was no significant effect on efficiency of bolus clearance, indicating a dose-related risk for impaired airway protection.

Although the incidence of pharyngeal dysfunction increased significantly during partial neuromuscular block, we were unable to detect changes in the integration of breathing and swallowing. Contrary to our hypothesis, swallowing remained within the expiratory phase in more than 90% of events regardless of neuromuscular block. No swallows occurred during inspiration. The respiratory-phase patterns in control recordings were similar to previous measurements in young adults,[23,24] but differed from studies showing that swallowing close to inspiration increases with age.[11,12] Inspiration immediately after swallowing combined with decreased pharyngeal clearance could increase the risk of aspiration. However, the incidence of pharyngeal dysfunction was not increased in the small subset of swallows that occurred in the transition between respiratory phases.

The brief period of apnea after swallowing is likely an important mechanism for protecting the airway from aspiration. In young individuals, the duration of postswallow apnea is short, supposedly representing a tight integration of the final part of pharyngeal swallowing and the resumption of breathing.[23,24,33] Our recordings of elderly in the control state revealed similar length of pre- and postswallow apnea as well as SAD compared with previous measurements in young adults.[23,24] However, in the young, SAD was shorter in spontaneous saliva swallows compared with bolus swallows.[23] This difference was less striking in the elderly. Speculatively, this could be an effect of altered sensory signaling with increasing age,[34] contributing to the prolonged SAD and postswallow apnea in elderly found by others.[11,14,17]

The temporal coordination of breathing and swallowing is governed by central pattern generators, colocalized within the brainstem.[35] Our findings indicate that partial neuromuscular block has limited impact on the central control of breathing and swallowing. This is reasonable because NMBAs poorly penetrate the blood–brain barrier.[36] However, we have previously in anesthetized patients found an effect on level of hypnosis by neuromuscular block.[37] In the current study, the self-reported estimate of vigilance (VAS-sedation) decreased during partial neuromuscular block. It is unlikely that this is centrally initiated, but rather due to reduced afferent signaling from muscles, described as the "afferentation theory."[38] Our results suggest that NMBAs cause pharyngeal dysfunction mainly by peripheral action on the pharynx.

The UES tone was markedly reduced at all levels of partial neuromuscular block, that is, even after recovery to an adductor pollicis TOF ratio greater than 0.90. The tonic contraction of the UES serves to prevent aerophagia and regurgitation and protects the airway against aspiration.[39] In addition, UES pressure oscillates with respiration,[23,39] adding further protection against regurgitation as the sphincter tone increases during inspiration when intrathoracic pressure decreases. The magnitude of respiratory UES variations was not affected by partial neuromuscular block, but occurred at a markedly lower mean UES pressure. This may impair airway protection at rest and during respiratory load. Moreover, aging is associated with increased airway collapsibility,[30] and partial neuromuscular block causes upper airway obstruction during forced inspiration.[18] The combination of low UES resting tone, a partially obstructed upper airway and increased inspiratory efforts, could undermine the margin of safety provided by the UES, thus increasing the risk of aerophagia, regurgitation, and aspiration.

The strikingly high incidence of pharyngeal dysfunction in control recordings of the elderly contrasts to previous data obtained in young adults using the same methodology. For illustration purposes, and based on reviewers' recommendations, key control data for young adults and elderly are summarized in table 4 and fig. 5. The historic nature of data obtained in the young mandates cautious interpretation. Although there were no major differences regarding the UES resting tone or in key components in respiratory-phase patterns of coordination of breathing and swallowing, the coordination of pharyngeal contraction and UES relaxation was faster in young adults. Hence, we speculate that the failed airway protection at control conditions in elderly is associated with a dysfunction in pharyngeal coordination.

Partial neuromuscular block affects the same key factors for pharyngeal function and airway protection in young and elderly (fig. 5); however, the severity of this impact was more pronounced in the elderly illustrating the accentuated vulnerability of elderly during recovery from neuromuscular block.

Interestingly, the incidence of coughing did not increase with the neuromuscular block-induced decline in pharyngeal function, not even in swallows with laryngeal penetration. This is in line with previous observations.[19,21,40] Consequences of impaired pharyngeal function and airway protection caused by NMBAs may be aggravated if the protective effects of coughing are hampered simultaneously. This also implies that cough may be an unreliable sign of pharyngeal dysfunction and aspiration in studies and in clinical practice.

Some limitations should be considered. Bolus administration through a syringe differs from normal drinking and could affect the preparatory stage of swallowing and possibly the incidence of pharyngeal dysfunction. However, as volunteers adapt, the incidence would decrease or remain stable as in the control group. As the incidence instead increased during partial neuromuscular block, our findings are not likely to be overestimated. Moreover, the study was neither placebo controlled nor was the order of targeted TOF ratios randomized. However, pharyngeal swallowing, once triggered, is considered reflexive

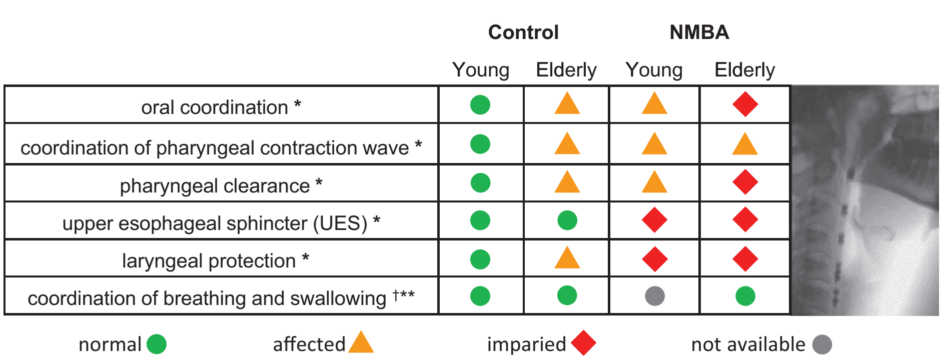

Fig. 5. Schematic presentation of key factors for normal pharyngeal function and airway protection and the impact of age and partial neuromuscular block. Oral coordination (prevents penetration of contents to the laryngeal inlet or aspiration); coordination of the pharyngeal contraction wave (the propagation of contractions in the pharyngeal constrictor muscles into the upper esophageal sphincter [UES]); pharyngeal clearance (prevents retention of pharyngeal residue after completion of the pharyngeal contraction wave); UES (resting pressure in the UES contributes to airway protection by preventing aerophagia and regurgitation); laryngeal protection (prevents penetration of contents to the laryngeal inlet or aspiration); coordination of breathing and swallowing (swallowing during expiration and normal duration and timing of apnea in relation to the pharyngeal phase of swallowing prevents aspiration); *Sundman *et al.*[21]; **Bodén *et al.*[22]; †Hårdemark Cedborg *et al.*[23] NMBA = neuromuscular-blocking agent.

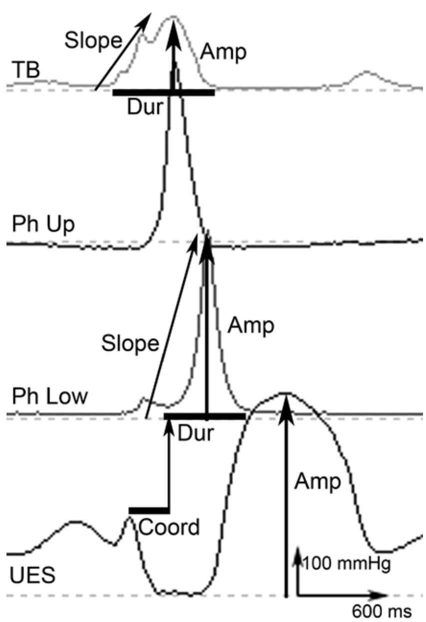

Fig. 6. Illustration of measurements of pharyngeal manometry reported in table 3. Amp = amplitude, maximum contraction pressure (mmHg); coord = coordination measured as the time between the start of pressure increase at Ph Low (Ph Low-start) and the start of UES relaxation (UES relaxation-start); Dur = contraction duration (ms); Ph Low = lower pharyngeal manometry transducer; Ph Up = upper pharyngeal manometry transducer; TB = tongue base; slope = contraction rate (mmHg/s); UES = upper esophageal sphincter.

and without voluntary control,[35] that is, placebo effects should be minimal. The order of TOF ratios was set to reflect clinical recovery although kept at steady state during measurements. After recovery to a TOF ratio of greater than 0.90, UES pressure was still reduced, in line with previous observations.[21,41,42] In young adults, atracurium caused residual pharyngeal muscle weakness that settled 15 min after recovery to TOF ratio greater than 0.90.[21] Hence, minor residual muscle weakness is expected at TOF ratios greater than 0.90. The study was not primarily designed to detect sex differences, and the lack of such differences should be interpreted with caution due to low-power analyzing subgroups. Although in the elderly, there was a tendency to a shorter time between pressure increase in the inferior pharyngeal constrictor muscle and UES relaxation at TOF ratio 0.70 compared with the resting control state, we could not confirm previous results in young adults during deeper partial neuromuscular block.[19,21]

Conclusion

Partial neuromuscular block in healthy elderly individuals cause an increased incidence of pharyngeal dysfunction, from 37 to 71%, with impaired ability to protect the airway. However, we were unable to detect an effect of partial neuromuscular block on the coordination of breathing and swallowing. Appropriate management of neuromuscular function including avoidance of residual neuromuscular block in the postoperative period is of utmost importance in the elderly.

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Competing Interests

Dr. Hårdemark Cedborg has received lecture fees from Abbott Scandinavia AB and AbbVie AB (Stockholm, Sweden). Dr. Sundman has received lecture fees from Abbott Scandinavia AB (Stockholm, Sweden) and Schering-Plough, now Merck Inc. (Whitehouse Station, New Jersey). Dr. Eriksson has received lecture fees and advisory honorarium from Abbott Scandinavia AB and AbbVie AB (Stockholm, Sweden) and Merck Inc. (Whitehouse Station, New Jersey). None of the other authors has any financial relationship with a commercial entity that has an interest in the subject of this article.

Correspondence

Address correspondence to Dr. Hårdemark Cedborg: Department of Anesthesia, Surgical Services, and Intensive Care, Karolinska University Hospital, 171 76 Stockholm, Sweden. anna.hardemark-cedborg@ki.se. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. 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
2. Murphy GS, Brull SJ: Residual neuromuscular block: Lessons unlearned. Part I: Definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg 2010; 111:120–8
3. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ: Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997; 41:1095–103
4. 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

5. 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; quiz 491–2
6. Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997; 86:765–71
7. Humbert IA, Robbins J: Dysphagia in the elderly. Phys Med Rehabil Clin N Am 2008; 19:853–66, ix–x
8. Butler SG, Stuart A, Castell D, Russell GB, Koch K, Kemp S: Effects of age, gender, bolus condition, viscosity, and volume on pharyngeal and upper esophageal sphincter pressure and temporal measurements during swallowing. J Speech Lang Hear Res 2009; 52:240–53
9. Butler SG, Stuart A, Leng X, Rees C, Williamson J, Kritchevsky SB: Factors influencing aspiration during swallowing in healthy older adults. Laryngoscope 2010; 120:2147–52
10. Butler SG, Stuart A, Markley L, Rees C: Penetration and aspiration in healthy older adults as assessed during endoscopic evaluation of swallowing. Ann Otol Rhinol Laryngol 2009; 118:190–8
11. Martin-Harris B, Brodsky MB, Michel Y, Ford CL, Walters B, Heffner J: Breathing and swallowing dynamics across the adult lifespan. Arch Otolaryngol Head Neck Surg 2005; 131:762–70
12. Shaker R, Li Q, Ren J, Townsend WF, Dodds WJ, Martin BJ, Kern MK, Rynders A: Coordination of deglutition and phases of respiration: Effect of aging, tachypnea, bolus volume, and chronic obstructive pulmonary disease. Am J Physiol 1992; 263(5 Pt 1):G750–5
13. Hirst LJ, Ford GA, Gibson GJ, Wilson JA: Swallow-induced alterations in breathing in normal older people. Dysphagia 2002; 17:152–61
14. Hiss SG, Treole K, Stuart A: Effects of age, gender, bolus volume, and trial on swallowing apnea duration and swallow/respiratory phase relationships of normal adults. Dysphagia 2001; 16:128–35
15. Martin-Harris B, Michel Y, Castell DO: Physiologic model of oropharyngeal swallowing revisited. Otolaryngol Head Neck Surg 2005; 133:234–40
16. Hiss SG, Strauss M, Treole K, Stuart A, Boutilier S: Effects of age, gender, bolus volume, bolus viscosity, and gustation on swallowing apnea onset relative to lingual bolus propulsion onset in normal adults. J Speech Lang Hear Res 2004; 47:572–83
17. Leslie P, Drinnan MJ, Ford GA, Wilson JA: Swallow respiratory patterns and aging: Presbyphagia or dysphagia? J Gerontol A Biol Sci Med Sci 2005; 60:391–5
18. 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
19. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, Kuylenstierna R: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: Simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997; 87:1035–43
20. Isono S, Ide T, Kochi T, Mizuguchi T, Nishino T: Effects of partial paralysis on the swallowing reflex in conscious humans. Anesthesiology 1991; 75:980–4
21. 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
22. Boden K, Cedborg AI, Eriksson LI, Hedström HW, Kuylenstierna R, Sundman E, Ekberg O: Swallowing and respiratory pattern in young healthy individuals recorded with high temporal resolution. Neurogastroenterol Motil 2009; 21:1163–e101
23. Hårdemark Cedborg AI, Bodén K, Witt Hedström H, Kuylenstierna R, Ekberg O, Eriksson LI, Sundman E: Breathing and swallowing in normal man—Effects of changes in body position, bolus types, and respiratory drive. Neurogastroenterol Motil 2010; 22:1201–8, e316
24. Hårdemark Cedborg AI, Sundman E, Bodén K, Hedström HW, Kuylenstierna R, Ekberg O, Eriksson LI: Co-ordination of spontaneous swallowing with respiratory airflow and diaphragmatic and abdominal muscle activity in healthy adult humans. Exp Physiol 2009; 94:459–68
25. Daniels SK, Schroeder MF, McClain M, Corey DM, Rosenbek JC, Foundas AL: Dysphagia in stroke: Development of a standard method to examine swallowing recovery. J Rehabil Res Dev 2006; 43:347–56
26. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J; 8th International Neuromuscular Meeting: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. Acta Anaesthesiol Scand 2007; 51:789–8
27. Langmore SE, Skarupski KA, Park PS, Fries BE: Predictors of aspiration pneumonia in nursing home residents. Dysphagia 2002; 17:298–7
28. Marik PE, Kaplan D: Aspiration pneumonia and dysphagia in the elderly. Chest 2003; 124:328–36
29. Taguchi A, Hyodo M, Yamagata T, Gyo K, Desaki J: Age-related remodeling of the hypopharyngeal constrictor muscle and its subneural apparatuses: A scanning electron microscopical study in rats. Dysphagia 2004; 19:241–7
30. Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo YL, White DP, Malhotra A: The influence of aging on pharyngeal collapsibility during sleep. Chest 2007; 131:1702–9
31. Feinberg MJ, Ekberg O: Videofluoroscopy in elderly patients with aspiration: Importance of evaluating both oral and pharyngeal stages of deglutition. AJR Am J Roentgenol 1991; 156:293–6
32. Matteo RS, Ornstein E, Schwartz AE, Ostapkovich N, Stone JG: Pharmacokinetics and pharmacodynamics of rocuronium (Org 9426) in elderly surgical patients. Anesth Analg 1993; 77:1193–7
33. Cherniack NS: Inspirational lessons from watching swallows. Exp Physiol 2009; 94:398–9
34. Aviv JE: Effects of aging on sensitivity of the pharyngeal and supraglottic areas. Am J Med 1997; 103(5A):74–6S
35. Jean A: Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiol Rev 2001; 81:929–69
36. Tassonyi E, Fathi M, Hughes GJ, Chiodini F, Bertrand D, Muller D, Fuchs-Buder T: Cerebrospinal fluid concentrations of atracurium, laudanosine and vecuronium following clinical subarachnoid hemorrhage. Acta Anaesthesiol Scand 2002; 46:1236–41
37. Ekman A, Stålberg E, Sundman E, Eriksson LI, Brudin L, Sandin R: The effect of neuromuscular block and noxious stimulation on hypnosis monitoring during sevoflurane anesthesia. Anesth Analg 2007; 105:688–95
38. Lanier WL, Iaizzo PA, Milde JH, Sharbrough FW: The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. Anesthesiology 1994; 80:392–401
39. Lang IM, Shaker R: Anatomy and physiology of the upper esophageal sphincter. Am J Med 1997; 103(5A):50–5S
40. Sundman E, Witt H, Sandin R, Kuylenstierna R, Bodén K, Ekberg O, Eriksson LI: Pharyngeal function and airway protection during subhypnotic concentrations of propofol, isoflurane, and

sevoflurane: Volunteers examined by pharyngeal videoradiography and simultaneous manometry. ANESTHESIOLOGY 2001; 95:1125–32

41. Eikermann M, Blobner M, Groeben H, Rex C, Grote T, Neuhäuser M, Beiderlinden M, Peters J: Postoperative upper airway obstruction after recovery of the train of four ratio of the adductor pollicis muscle from neuromuscular blockade. Anesth Analg 2006; 102:937–42
42. 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

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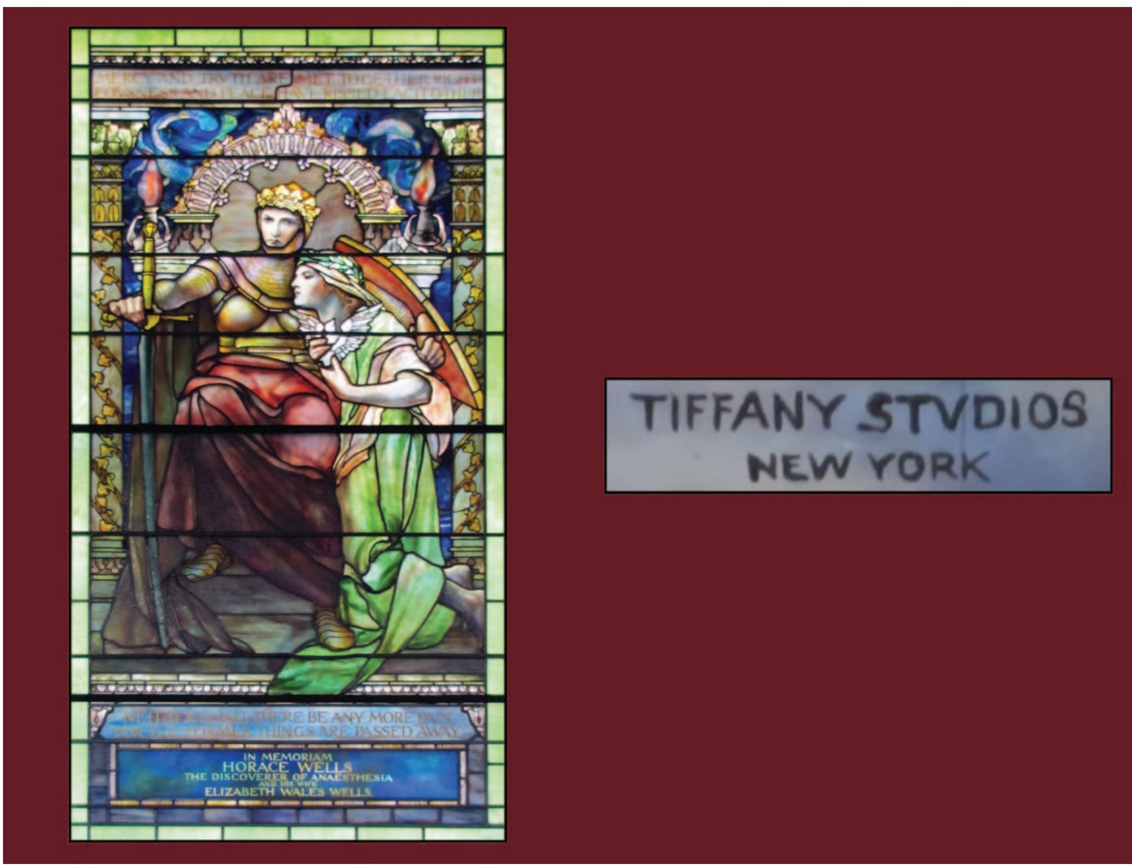
Tiffany's Stained Glass Memorial to Dr. and Mrs. Horace Wells: *Righteousness and Peace*



In 1903 Louis Comfort Tiffany designed a memorial stained glass window (*left*), the bottom of which is dedicated "IN MEMORIAM / HORACE WELLS / THE DISCOVERER OF ANAESTHESIA / AND HIS WIFE / ELIZABETH WALES WELLS." Just above that dedication run the words: "NEITHER SHALL THERE BE ANY MORE PAIN / FOR THE FORMER THINGS ARE PASSED AWAY." The top of the window reads: "MERCY AND TRUTH ARE MET TOGETHER RIGHT- / EOUSNESS AND PEACE HAVE KISSED EACH OTHER." Known simply as "Righteousness and Peace," the window was commissioned in 1903 by Horace and Elizabeth Wells' son, Charles Thomas Wells, for installation at the First Church of Christ in Hartford, Connecticut. (Copyright © the American Society of Anesthesiologists, Inc.)

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.