The Incidence and Mechanisms of Pharyngeal and Upper Esophageal Dysfunction in Partially Paralyzed Humans

Pharyngeal Videoradiography and Simultaneous Manometry after Atracurium

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Background: Residual neuromuscular block caused by vecuronium alters pharyngeal function and impairs airway protection. The primary objectives of this investigation were to radiographically evaluate the swallowing act and to record the incidence of and the mechanism behind pharyngeal dysfunction during partial neuromuscular block. The secondary objective was to evaluate the effect of atracurium on pharyngeal function.

Methods: Twenty healthy volunteers were studied while awake during liquid-contrast bolus swallowing. The incidence of pharyngeal dysfunction was studied by fluoroscopy. The initiation of the swallowing process, the pharyngeal coordination, and the bolus transit time were evaluated. Simultaneous manometry was used to document pressure changes at the tongue base, the pharyngeal constrictor muscles, and the upper esophageal sphincter. After control recordings, an intravenous infusion of atracurium was administered to obtain train-of-four ratios (T4/T1) of 0.60, 0.70, and 0.80, followed by recovery to a train-of-four ratio of more than 0.90.

Results: The incidence of pharyngeal dysfunction was 6% during the control recordings and increased (P < 0.05) to 17%, and 20% at train-of-four ratios 0.60, 0.70, and 0.80, respectively. After recovery to a train-of-four ratio of more than 0.90, the incidence was 13%. Pharyngeal dysfunction occurred in 74 of 444 swallows, the majority (80%) resulting in laryngeal penetration. The initiation of the swallowing reflex was impaired during partial paralysis (P = 0.0081). The pharyngeal coordination was impaired at train-of-four ratios of 0.60 and 0.70 (P < 0.01). A marked reduction in the upper esophageal sphincter resting tone was found, as well as a reduced contraction force in the pharyngeal constrictor muscles. The bolus transit time did not change significantly.

Conclusion: Partial neuromuscular paralysis caused by atracurium is associated with a four- to fivefold increase in the incidence of misdirected swallowing. The mechanism behind the pharyngeal dysfunction is a delayed initiation of the swallowing reflex, impaired pharyngeal muscle function, and impaired coordination. The majority of misdirected swallows resulted in penetration of bolus to the larynx. (Key words: Dysphagia; postoperative pulmonary complications; respiration.)

THE incidence and the underlying mechanism of pharyngeal dysfunction among anesthetized patients are unknown, although failed maintenance of the airway has been shown to be one of the most frequent anesthesia-related causes of injury or death in the immediate postoperative period.1,2

Simultaneous videomanometry combines video recordings of fluoroscopically visualized contrast bolus swallows, videoradiography, and simultaneous solid-state manometry of the pharynx and upper esophagus.3 This makes it possible to detect pathologic swallowing patterns; that is, dysfunction at various levels in the pharynx, laryngeal inlet, and upper esophagus by fluoroscopy, and to simultaneously monitor the muscular function in different parts of the pharynx and esophagus by manometry. The method previously has been used to study normal swallowing patterns4 and to examine patients with a history of dysphagia of different origin.1–6
Residual effects of anesthetic agents may have serious effects on pharyngeal function, airway protection, and pulmonary function. Recently, Berg et al. showed an increased incidence of postoperative pulmonary complications in patients with residual neuromuscular block caused by pancuronium. In a recent study,8 we showed that mechanical adductor pollicis train-of-four (TOF) ratios less than 0.90 as a result of administration of vecuronium were associated with impaired pharyngeal muscle coordination, a reduced resting tone in the upper esophageal sphincter (UES) muscle, and episodes of contrast penetrating to the laryngeal inlet. In that study,8 no detailed analysis of the video recorded fluoroscopy of the pharynx, upper esophagus, and laryngeal inlet was performed.

The primary objectives of this investigation were to radiographically evaluate the swallowing act during partial neuromuscular block and to record the incidence of and the mechanism behind pharyngeal dysfunction during different levels of partial neuromuscular block. The secondary objective was to evaluate the effect of atracurium on pharyngeal function and airway protection.

Materials and Methods

Twenty healthy volunteers (12 men and 8 women) aged 24–49 yr were included after informed consent and approval of the Local Ethical Committee of Human Research at Karolinska Hospital and Institute, Stockholm, Sweden. None had undergone surgery of the pharynx, upper esophagus, or the upper airway. They were not prescribed medication and had no history of dysphagia, gastroesophageal reflux, or neuromuscular, liver, or renal disease.

After 4 h of fasting, the participants were placed in the right lateral position on a radiography table with a 15° head-up tilt. Peripheral arterial oxygen saturation, standard routine electrocardiographic data, and systemic blood pressure were monitored. An intravenous cannula was placed in a left cubital vein, and a continuous infusion of normal saline was administered at a rate of 100–200 ml/h.

Videomanometry

The video-recorded fluoroscopic field covered the oral cavity, soft palate, laryngeal inlet, and pharyngoesophageal segment in lateral projection. A manometry catheter with four solid-state pressure transducers separated by 2 cm (Konigsberg Instruments, Pasadena, CA) was used. The two distal sensors recorded pressure changes circumferentially, the two proximal sensors at a 180° angle. The catheter was introduced through one nostril and advanced to place the tip in the proximal part of the esophagus. Correct catheter position was achieved and subsequently confirmed using intermittent fluoroscopy. The most distal sensor was placed at the level of the UES, making the other sensors register the pressure changes at the pharyngeal constrictor muscles and at the base of the tongue.

During series of five bolus swallows of 10 ml contrast medium (Omnipaque, 240 mg iodine/ml, Nycomed, Oslo, Norway), the fluoroscopic and manometric registrations were recorded simultaneously on a videotape equivalent to 50 half-frames/s. The series of swallows were repeated on five separate occasions: an initial series of control recordings and then during a steady state infusion of atracurium targeting mechanical adductor pollicis TOF ratios of 0.60, 0.70, and 0.80, after which the infusion was discontinued and a final series of swallows was recorded after recovery to a TOF ratio of more than 0.90.

The video recordings of the fluoroscopic images were interpreted by an experienced radiologist. Although the radiologist was not aware of the level of neuromuscular block, the interpretation was not made with the radiologist strictly blinded because the different TOF ratios followed sequentially.

Each contrast bolus swallow was evaluated radiographically to detect normal and abnormal swallowing patterns. The videoradiography was analyzed for the following types of pharyngeal dysfunction: inability to retain the bolus of contrast in the mouth with premature leakage or into the pharynx; misdirected swallowing; that is, penetration of contrast medium to the laryngeal vestibule, either to its superior portion or to the vocal cords or into the trachea; or retention of contrast medium in the pharynx after completion of the swallowing act. The video recordings also were analyzed to study the interactions between different muscle groups in the pharynx during swallowing. The initiation of the pharyngeal stage of swallowing was evaluated as 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 (initiation [milliseconds]). The transportation (bolus transit time [milliseconds] i.e., the interval between the times at which the bolus head passed the anterior faucial arches and the bolus tail and the constrictor wave reached the UES) was also measured.

The manometric analysis was made as described in our previous work. The UES resting tone (mmHg) was mea-
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Table 1. Mechanical Adductor Pollicis TOF Ratios and T1

<table>
<thead>
<tr>
<th>Set Value</th>
<th>TOF Ratio*</th>
<th>T1 (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.60</td>
<td>0.61 (0.03)</td>
<td>93 (1.2)</td>
</tr>
<tr>
<td>0.70</td>
<td>0.70 (0.02)</td>
<td>96 (1.3)</td>
</tr>
<tr>
<td>0.80</td>
<td>0.80 (0.02)</td>
<td>99 (1.4)</td>
</tr>
<tr>
<td>&gt;0.90</td>
<td>0.95 (0.03)</td>
<td>100 (1.4)</td>
</tr>
<tr>
<td>Control</td>
<td>0.99 (0.03)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD.

* T4/T1.
† Percentage of control T1 height.

TOF = train-of-four.

Table 2. Pharyngeal Dysfunction

<table>
<thead>
<tr>
<th>Premature Leakage of Contrast from Mouth to Pharynx</th>
<th>Penetration of Contrast to the Laryngeal Inlet</th>
<th>Incomplete Bolus Clearance, Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>59</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are parts of total count of swallows with pharyngeal dysfunction (n = 74).

for the experiment was approximately 1.5 h. For three of the studied subjects, the experiment was extended, with recordings 15 and 30 min after recovery to a TOF ratio of more than 0.90. The number of swallows recorded at these occasions was limited and therefore not included in the statistical analysis.

Statistics

All videomanometric variables were analyzed against TOF ratios using regression for each individual followed by t test for the mean regression coefficient of the group. The Wilcoxon signed rank test was used to detect differences between measurements at a TOF ratio more than 0.90 and control. For both the t test and the Wilcoxon signed rank test, probability values < 0.05 were considered significant. Data are presented as the mean and SD. For the initiation of the swallowing process, data are presented as box plots with 25–75% quartiles because we could not confirm a normal distribution of that variable.

Results

Fluoroscopy

A total of 444 swallows was analyzed. In the control recordings, 6% of swallows showed signs of pharyngeal dysfunction. The incidence of pharyngeal dysfunction was markedly increased (regression analysis, P = 0.0039) during partial paralysis; that is, to 28% at an adductor pollicis TOF ratio of 0.60, 17% at a TOF ratio of 0.70, and 20% at a TOF ratio of 0.80. Even after recovery to a TOF ratio of 0.90 or more there was a minor increase in the incidence of pharyngeal dysfunction to 13% (Wilcoxon signed rank test, P = 0.038).

In pooling all swallows with pharyngeal dysfunction (74 of 444), it was found that the majority, 59 of 74 (80%), resulted in misdirected swallowing, with contrast medium reaching to the level of the vocal cords. There were 12 episodes of premature leakage to the pharynx and 3 of incomplete bolus clearance with retention of pharyngeal content (table 2). In evaluating the underlying...
ing mechanism, we found an impairment of the initiation of the swallowing process at all levels of neuromuscular block. This was a result of a delayed start of the hyoid bone movement (regression analysis, $P = 0.0081$; fig. 1). Swallows with pharyngeal dysfunction, regardless of TOF ratio, showed a tendency to delayed hyoid bone movement, compared with those without pharyngeal dysfunction, though this was not statistically significant. The bolus transportation, i.e., bolus transit time, was not significantly changed ($P = 0.36$), comparing the control registrations (mean, 737 ms; SD, 57 ms) with a TOF ratio 0.60 (mean, 763 ms; SD, 124 ms).

**Manometry**

Partial paralysis caused marked changes in the manometry of the pharynx and upper esophagus.

The coordination of the pharyngeal and esophageal muscles was significantly impaired (regression analysis, $P = 0.0054$), with a reduced time interval between the contraction of the PHCI and the relaxation of the UES at TOF ratios less than 0.80 (fig. 2).

The UES resting tone was markedly reduced (regression analysis, $P < 0.001$) during partial paralysis. Even after recovery to TOF ratios more than 0.90, there was a still a minor reduction in the resting tone (Wilcoxon signed rank test, $P = 0.0026$; fig. 3). Moreover, the PHCI pressure recordings revealed a reduced peak contraction amplitude and contraction slope, even after recovery to TOF ratios more than 0.90 (Wilcoxon signed rank test, $P < 0.01$; fig. 4). The pressure recordings at the base of the tongue revealed a reduced contraction slope at TOF ratios 0.90 or less (Wilcoxon signed rank test, $P = 0.0045$); the peak contraction amplitude was reduced only at a TOF ratio of 0.60.
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Fig. 4. Pharyngeal constrictor muscle function during partial paralysis. Contraction peak amplitude (mmHg), slope of contraction curve (mmHg/s) and duration of contraction (ms). All variables versus train-of-four (TOF) ratio. Mean ± 1 SD, *P < 0.01. (Regression for each individual followed by t test for the mean regression coefficient of the group. The Wilcoxon signed rank test was used to detect differences between a TOF ratio > 0.90 and control.)

The duration of contraction did not change significantly for any of the studied muscles in the pharynx or upper esophagus.

Exclusions from the Study
Two volunteers (one man and one woman) were excluded from the study because of frequent uncontrolled swallows during the control recordings and because they found the test situation stressful. None of the remaining volunteers reported swallowing difficulties during the control recordings, and none found the study stressful. During partial relaxation the volunteers reported subjective difficulty in swallowing, blurred vision, and difficulty to articulate. However, none found the partial relaxation uncomfortable or stressful.

A total of 444 swallows was analyzed in the remaining 18 volunteers; that is, we were not able to analyze six swallows because of either misplaced manometry catheter or disturbed manometric or videoradiographic recording. Finally, another 29 swallows were analyzed from the three subjects also studied 15 and 30 min after recovery to a TOF ratio of more than 0.90.

Discussion
Radiology allows analysis of movement of several pharyngeal anatomic structures. The current study shows fundamental changes in movement of crucial anatomic structures during partial paralysis. The main finding of this study was a delayed initiation of the swallowing process and an impaired coordination of the pharyngeal muscular activity during partial neuromuscular block. An adductor pollicis TOF ratio of 0.90 or less was associated with impaired pharyngeal function and airway protection, resulting in a four- to fivefold increase in the incidence of pharyngeal dysfunction causing misdirected swallowing. Moreover, pharyngeal function and airway protection may be impaired, even if the adductor pollicis muscle has recovered to a TOF ratio of more than 0.90.

In a previous study, we showed that mechanical adductor pollicis TOF ratios less than 0.90 induced by vecuronium were associated with impaired pharyngeal muscle coordination, a reduced resting tone in the UES muscle, and aspiration episodes. In that investigation, the evaluation was focused on manometry, except for radiographically measured transit time and determination of the number of individuals with aspiration episodes. No detailed analysis of the video recorded fluoroscopy was performed, which is necessary for understanding of the pharyngeal function and underlying mechanisms of pharyngeal dysfunction.
Normal Swallowing

Swallowing is made up of a voluntary oral stage, an automatic pharyngeal stage, and an autonomic esophageal stage. The oral stage of swallowing includes ingestion, processing, and formation of a bolus. The bolus is then transferred on the tongue blade toward the pharynx. Initiation of pharyngeal swallowing is considered to be elicited at the level of the anterior faucial arches. This critical event can be recognized easily on lateral radiograms of the neck as the distinct anterior movement of the hyoid bone. The pharyngeal stage of swallowing includes closure of the airways and transportation of the bolus through the pharynx into the esophagus. The esophageal stage of swallowing includes transportation of the bolus into the stomach. These stages evaluated by fluoroscopy are shown schematically in figure 5. This study was concerned particularly with the oral and pharyngeal stages of swallowing and the protection of the upper airway.

Pharyngeal Dysfunction

Any part of the bolus found in the laryngeal vestibule or airways is abnormal, especially if this occurs during a test situation in which the control recording is normal. However, in a previous study it was shown that misdirected swallowing into the subepiglottic portion of the laryngeal vestibule was seen in 5% of nondysphagic adults. Of patients referred for radiologic evaluation because of dysphagia, another study showed that 23% had penetration of contrast to the laryngeal vestibule or the trachea. In the current study, we found an incidence of pharyngeal dysfunction in partially paralyzed, awake volunteers of approximately 20-30%; that is, a four- to fivefold increased incidence of pharyngeal dysfunction compared with the normal situation. Interestingly, this increase in pathologic swallows resulted mainly from misdirected swallows with penetration of bolus into the laryngeal vestibule. The function of the vocal cords in preventing the bolus from entering the trachea was intact in all volunteers. The intact competence of the larynx to protect the trachea from aspiration in this study may be caused by the relative resistance of the vocal cords to muscle relaxants.

Laryngeal elevation during swallowing is essential for closure of the laryngeal aperture and opening of the pharyngoesophageal junction. The finding that the hyoid bone movement was delayed during partial paralysis means that laryngeal elevation during swallowing was impaired by partial paralysis. This agrees with previous reports evaluating effect of partial paralysis on suprahy-
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oid bone muscles, such as geniohyoid and mylohyoid muscles.11 A delayed start of the hyoid bone movement results in an increased risk of bolus penetrating to the larynx because the bolus remains longer in the upper pharynx with the laryngeal aperture open. Furthermore, the coordination of the PHCI and the UES was impaired, resulting in a shorter duration of time for the UES to relax and be prepared to receive the bolus. The total transit time for the bolus is a less precise measurement and was, in this study, not significantly changed during partial neuromuscular block, as opposed to the results of the previous one.6

Interpretation of Data and Statistical Analysis
For all variables, the statistical analysis was initiated with a regression versus TOF ratios for each individual subject and variable. This was followed by a t test for the mean regression coefficient of the group. If the regression coefficient was not equal to 0 (P < 0.05), we used the Wilcoxon signed rank test to determine whether the measurements at TOF ratio more than 0.90 were different from the control recordings. This is a very robust test, and it could be argued that, for those variables where changes could be statistically shown only at TOF ratios 0.60 and 0.70, there may well be a difference even after further recovery.

The regression lines are close to straight lines, except for the UES resting pressure, which is better described as exponential. It cannot, however, be excluded that the true shape of the curve is sigmoid. Therefore, it could be argued that if a larger number of volunteers had been examined, it would be possible to show differences even after further recovery. However, with the available mechanomyographic equipment it is not possible to study the interval between recovery to TOF ratios more than 0.90 and the control recordings with higher precision. Also, for ethical reasons, we hesitate to study laryngeal dysfunction and risk of aspiration in volunteers during more profound neuromuscular block than TOF ratio 0.60.

After having accomplished the major part of the study, we could see that the UES resting tone was still reduced at TOF ratios more than 0.90. We therefore extended the study with recordings 15 and 30 min later for three of the participants. The number of swallows recorded at these occasions obviously is limited. However, we could see that 15 min after recovery to a TOF ratio of more than 0.90 the UES resting tone approximated control values, 60 versus 80 mmHg at control. The incidence of pharyngeal dysfunction was 7% 15 min after recovery to a TOF ratio of more than 0.90, but it must be taken into account that the number of swallows recorded is limited.

Different Drugs Affecting the Upper Esophageal Sphincter and the Inferior Pharyngeal Constrictor Muscle
There was a pronounced decrease in the UES resting tone during partial paralysis; that is, even after recovery to a TOF ratio of more than 0.90. In a previous study with vecuronium, there was no such influence after recovery to TOF ratios of more than 0.90.6 We also found a reduced peak contraction amplitude for the PHCI, along with a reduced slope of the contraction curve. In the previous study using vecuronium for partial paralysis,6 we did not find a significant affection of the pharyngeal constrictor muscle. The technique used to measure UES and PHCI activity was the same as in this study. This could represent different sensitivity of pharyngeal muscles to atracurium and vecuronium. However, no comparative study has been performed in this way.

Exclusions from the Study
Two subjects found the test situation to be stressful and had to be excluded. Consequently, it may be argued that the test situation in itself may influence the pharyngeal and esophageal function during swallowing. However, none of the remaining 18 volunteers reported swallowing difficulties during the control recordings, and none of them found the study to be stressful. Moreover, the incidence of pharyngeal dysfunction during the control recordings was in agreement with previous reports.9 We therefore regard the presented results from the remaining 18 volunteers as reliable.

Clinical Implication of Disturbed Swallowing Pattern
Three important findings of pharyngeal dysfunction are inability to retain the bolus in the mouth, with premature leakage to the pharynx; misdirected swallowing; and retention of bolus in the pharynx after completion of the swallowing act. Although 14 of 18 volunteers had one or several events of misdirected swallowing during partial paralysis, none of the episodes led to aspiration below the level of the vocal cords. For technical reasons all volunteers were examined while in the right lateral position. We do not know what the results would have been if subjects had been performed with the subjects supine. The studied subjects were also examined while awake, with no drugs other than atracurium administered. It has been shown previously that sedation and analgesia affect the swallowing reflex.12,13 The UES resting tone is enhanced by stress14; it decreases during sleep.15 Moreover, our stud-
ied group of volunteers consisted of young healthy individuals. Elderly individuals (> 65 yr of age) have a lower UES resting tone than do younger controls. Furthermore, in elderly persons, the UES resting tone does not respond to esophageal air and balloon distention, which shows an impaired sphincter function. It has even been shown that of nondysphagic elderly patients older than 72 yr, only 16% had normal videoradiographic examinations of swallowing; as many as 65% showed varying degrees of misdirected swallowing. This observation makes the results of the current study even more important because it is possible that partial neuromuscular paralysis in elderly patients with already impaired pharyngeal function may aggravate the pharyngeal impairment and lead to even more profound pharyngeal dysfunction, including aspiration. With this in mind, it seems likely that the pharyngeal function among postoperative patients could be even more impaired than in our studied group of awake volunteers.

A reduction in the UES resting tone may facilitate regurgitation, but to our knowledge it has not been associated with misdirected swallowing. The UES resting tone is a variable that is easy to measure and seems to be very sensitive to partial neuromuscular block. However, the UES is only one part of the pharynx, and changes in its resting tone alone may not be responsible for the pharyngeal dysfunction during swallowing. Conversely, our results suggest that return of the UES resting tone to normal values is associated with a normal function of the pharynx. The reduction of the UES resting tone seems to be an indicator of pharyngeal dysfunction and its return to normal values an indicator of normalizing function of the pharynx and the upper airway protection.

Conclusion

Partial neuromuscular paralysis resulting from administration of atracurium is associated with a four- to fivefold increase in the incidence of misdirected swallowing. The mechanisms behind the pharyngeal dysfunction are a delayed initiation of the swallowing reflex, impaired pharyngeal muscle function, and impaired coordination. The majority of misdirected swallows resulted in penetration of bolus to the larynx.

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