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Recovery of Airway Protection Compared with Ventilation in Humans after Paralysis with Curare

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d-Tubocurarine (dTc) was administered intravenously to six healthy unanesthetized volunteers to assess the sensitivity to neuromuscular blockade of those muscles involved in protecting the airway against obstruction and/or aspiration relative to the muscles of inspiration. Each subject was given an intravenous bolus of dTc followed by an infusion to allow three different levels of inspiratory muscle weakness as measured by maximum inspiratory pressure (MIP). Levels of MIP were control (−90 cm H_2O), −60, −40, and −20 cm H_2O. Vital capacity (VC), hand grip strength (HGS), and end-tidal CO_2 (PET_{CO_2}) were obtained at each level. At each level of weakness and at intermediate values during recovery, muscles of airway protection were functionally assessed by noting the MIP at which the maneuver could be accomplished and the MIP at which they could not. The mean of these two values was calculated for each subject. The tests were: 1) ability to swallow, 2) ability to perform a valsalva maneuver, 3) prevent obstruction of the airway, and 4) ability to approximate teeth. These were compared with head lift and straight leg raising. At maximum neuromuscular blockade (MIP of −20 cm H_2O), VC was 2.0 liters, HGs was 0, and PET_{CO_2} was normal. Muscles of airway protection were still incapacitated. Swallowing returned above MIP of −43 cm H_2O, approximation of teeth above −42 cm H_2O, airway obstruction above −39 cm H_2O, and valsalva above −33 cm H_2O. Thus, although ventilation may be adequate at MIP = −25 mmHg, the muscles of airway protection are still nonfunctional. Further reversal of neuromuscular blockade must be accomplished before a patient whose trachea is extubated can protect the airway. All subjects who could accomplish a head lift could perform the airway protective maneuvers. (Key words: Airway: obstruction; protection. Neuromuscular relaxants: d-tubocurarine. Ventilation: maximum inspiratory pressure (MIP).)

RESIDUAL RESPIRATORY MUSCLE weakness is always a concern in patients who have received muscle relaxants. Satisfactory return of muscle function, particularly of the inspiratory muscles, must be assured prior to allowing patients to breathe spontaneously, and before one can assume that a patient can maintain a patent airway. Wescott *et al.*[1] proposed the use of maximum inspiratory pressure (MIP) as an index of the ability of the patient to breathe adequately and as an indication of ventilatory reserve. Several studies have shown that a maximal inspiratory pressure of −25 cm H_2O was consistent with inspiratory muscle power sufficient to maintain a "normal" level of minute ventilation.[1,2] However, the indications for tracheal intubation include not only ventilatory insufficiency, but also the ability to protect the patient's airway against aspiration or obstruction.

Although several studies, most recently those of Gal,[3,4] suggest sparing of the diaphragm relative to peripheral muscles of the forearm, there are few data describing the relative sensitivity to nondepolarizing relaxants of muscles involved in swallowing, vocal cord closure, or elevating the tongue away from the posterior pharyngeal wall. The purpose of this study was to establish the sensitivity to d-tubocurarine (dTc) of those muscles involved in protecting the airway against obstruction and/or aspiration relative to the muscles of ventilation, and other peripheral muscle groups.

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Materials and Methods

The protocol for this study was approved by the University of Washington Committee for Human Research. Six healthy subjects, five men and one woman, ages 25–35 yr, took part in this study. After signing a consent form, each subject came to the laboratory having fasted overnight. After an intravenous catheter was inserted, esophageal and gastric balloons were positioned and subjects were positioned supine for the study. Atropine, 0.4 mg iv and 0.4 mg im, were administered to reduce oral secretions.

During the study period, each subject breathed through a mouthpiece, with the nasal passages occluded by a nose clip. Tidal volume (V_T) and end-tidal CO_2 (PET_{CO_2}) were monitored continuously throughout the experiment utilizing a Fleish Pneumotachograph and infrared CO_2 analyzer (Beckman), respectively. At intervals, vital capacity (VC) was measured with a Collins spirometer and maximum inspiratory pressure (MIP) was obtained by having the subject make a maximum inspiration effort at func-

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tional residual capacity (FRC) against a closed airway, while airway pressure was measured with a calibrated aneroid manometer (Bourns). To establish strength of peripheral muscles, hand grip strength (HGS) was assessed using a hand grip dynameter (Bourns); "head lift" (the ability of the subject to raise the head from the bed and sustain life for 5 s) and straight leg raising (the ability to maintain elevation of the lower extremity for 5 s) were also tested at the same time.

Muscles of the airway were clinically assessed as follows:

1. *Ability to Swallow.* The subject was asked to swallow and indicate whether he or she could perform the maneuver. The swallow was confirmed on the esophageal balloon pressure tracing.
2. *The Ability to Approximate the Vocal Cords.* The subject was asked to perform a Valsalva maneuver to an esophageal pressure of +30 cm H_2O. When too weak to perform this maneuver, manual abdominal pressure was applied by the investigator. The presence of a leak past the cords was assessed clinically and documented by measuring air flow at the mouth.
3. *Ability to Maintain a Patent Airway.* The point at which the subject's tongue fell into the oropharynx was noted. This was not a subtle sign, because it was indicated by complete airway obstruction if the subject's mandible was not elevated (jaw thrust) by one of the investigators.
4. *The Subject's Ability to Elevate His/Her Own Mandible.* This was assessed by noting the ability to approximate there incisors. All measurements described above were made in the baseline control state, and at intervals thereafter as designated by the level of MIP attained during the administration of and recovery from dTc.

After baseline control measurements were obtained, dTc was administered intravenously in 3-mg increments until predetermined target values of MIP of −60, −40, and −20 cm H_2O were attained. After reaching each of these levels of paralysis, a constant level of muscle relaxation during the measurements was maintained by continuous intravenous infusion of dTc. The average total dose of dTc administered throughout a single study was 31 mg (approximately 12 mg by infusion), but the dose required varied from subject to subject. At each of the three predetermined MIP, VC, HGS, $P_{ET_{CO_2}}$ were measured. At these and intermediate levels of relaxation, MIP, head lift, leg lift, and tests of muscles of airway protection were performed. Tests were done both during the phase of increasing muscle paralysis as well as during recovery. No systematic differences were noted between values obtained during onset of recovery from those obtained following recovery from the deepest level of paralysis.

The lowest MIP at which a subject could perform a specific maneuver, *e.g.*, head lift, and the highest MIP at which the subject could not perform the maneuver were noted; the "MIP_{50}" at which there was a change in the subject's ability to perform a particular maneuver was then calculated as the mean value of the former two levels of MIP. (This is similar to establishing a MAC value for an anesthetic.) For all subjects and all maneuvers, the largest difference between the MIP at which a maneuver could be done, and the one at which it could not, was 10 cm H_2O. These MIP_{50}s were then averaged for all subjects and their standard errors calculated.

Statistical analysis was carried out to determine if the MIP_{50} for each test was different from −25 cm H_2O. The t value was calculated for the MIP_{50} for each test and compared with −25 cm H_2O utilizing Student's t test. A P value of $<.05$ was accepted as denoting statistical significance.

Multiple t tests can lead to the conclusion that differences were significant when, in fact, the samples may come from the same normal population. That is, if 20 groups drawn from the same population were tested for differences, then significance ($P < 0.05$) would be expected once. The probability of this type of error, $P_n(k)$, can be calculated as follows: If P is the probability of an event occurring (significance level), n the number of times the test was performed, and k the number of times significance was found, then

$$P_n(k) = \frac{n!}{k!(n-k)!} P^k(1-P)^{n-k},$$

where n! is n factorial [$n = n \cdot (n-1)(n-2) \ldots 2.1$].[5] We accepted a 5% probability of an error of this type.

Results

dTc spared the muscles of ventilation relative to peripheral muscles involved in hand grip (fig. 1). At low doses of dTc, a MIP of −63 cm H_2O was associated with no change in VC but a 60% reduction of hand strength. At the most profound level of weakness (MIP = −20), VC was reduced to 35% of control. However, even at this level, VC was still 2.0 L, indicating some ventilatory reserve over and above that needed to maintain a normal tidal volume. $P_{ET_{CO_2}}$ was normal and constant throughout the study, indicating adequate spontaneous ventilation at MIP = −20. Hand grip was abolished at this level.

Of the muscle groups tested, head lift and leg raising were affected earliest by dTc when compared with maximal inspiratory pressure (MIP_{50} of 53 ± 2.4 and 50 ± 2.8, respectively) (fig. 2). Of the airway tests studied, both the ability to swallow and to approximate the teeth (elevate mandible) were sensitive to dTc with a mean MIP_{50} ± (SEM) of −42 ± 4.8 and −43 ± 5.3 cm H_2O, respectively. We were impressed that the ability to elevate the glottis, observed visually, did not correspond with actual completion of the swallowing maneuver demonstrated by

esophageal pressure measurements. Complete aiway obstruction caused by the tongue occluding the oropharynx occurred at a MIP_{50} of -39 ± 4.9 cm H_2O necessitating elevation of the mandible by an investigator for the duration of experiment.

The ability to approximate the vocal cords and withstand a pressure of +30 cm H_2O was present at MIP greater than (more negative) above -33 ± 4.4 cm H_2O, the value usually acknowledged as indicating adequacy of ventilatory reserve. The MIP_{50}s for the clinical tests of muscle function were significantly greater than -25 cm H_2O with P values $< .001$ for head lift and straight leg raising; $<.02$ for swallowing, airway obstruction, and ability to approximate the teeth; and $<.05$ for performing the valsalva maneuver. The probability ($P_n(k)$) that, by doing multiple t tests, we were in error in claiming significant differences from -25 cm H_2O in our values was less than .000001.

All subjects who could sustain a head lift were able to perform all of the airway protective maneuvers.

After the study, the subjects stated they did not feel dyspneic, but universally expressed anxiety at times of airway obstruction and particularly at the inability to swallow secretions. At MIP of -20 cm H_2O, paradoxical respirations were noted.

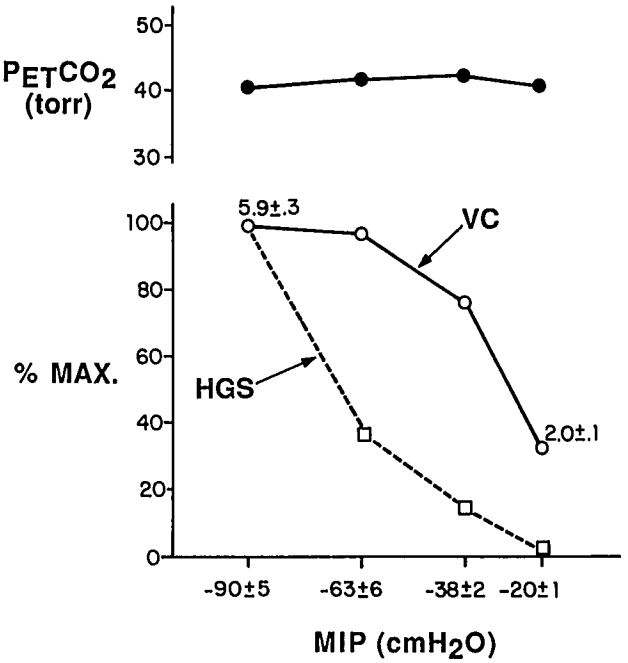

FIG. 1. Hand grip strength (HGS), vital capacity (VC), and end-tidal P_{CO_2} at three different levels of paralysis with dTc measured by maximum inspiratory pressure (MIP). At the lowest level of MIP (-20 cm H_2O), HGS is absent, but ventilation is adequate and VC indicates ventilatory reserve. Number labels on VC curve indicate actual values (in liters) for VC plus or minus SE

Discussion

In this study, we have shown that the muscles responsible for airway protection may be nonfunctional in the presence of nondepolarizing muscle relaxants when ventilation is adequate. Most previous studies have concentrated on measurements of adequacy of pulmonary function as an indication of reversal of blockade from nondepolarizing muscle relaxants.

Wescott *et al.* recognized that clinical judgement alone might not be adequate in assessing ventilatory adequacy after anesthesia, in particular when muscle relaxation with dTc had been utilized.[1] In addition, the concept was proposed that adequate ventilation alone was not sufficient, but that some degree of ventilatory reserve should be present. Thus, deeper breaths could be taken to facilitate coughing, and prevention or reversal of atelectasis. Furthermore, increased ventilatory requirements might be required to meet increased metabolic demands in the postoperative period. Based on observations in humans and in dogs, Wescott[1] and Bendixen *et al.*[6] established that ventilatory capacity sufficient to maintain normal Pa_{CO_2} correlated with a negative inspiratory pressure of -10 to -16 cm H_2O. Thus, a "reserve" of double this value (-20–-30 cm H_2O) would allow for deeper breaths and increased ventilation. A value of -25 cm H_2O has thus become accepted as the standard value above which a patient with normal lungs recovering from paralysis with

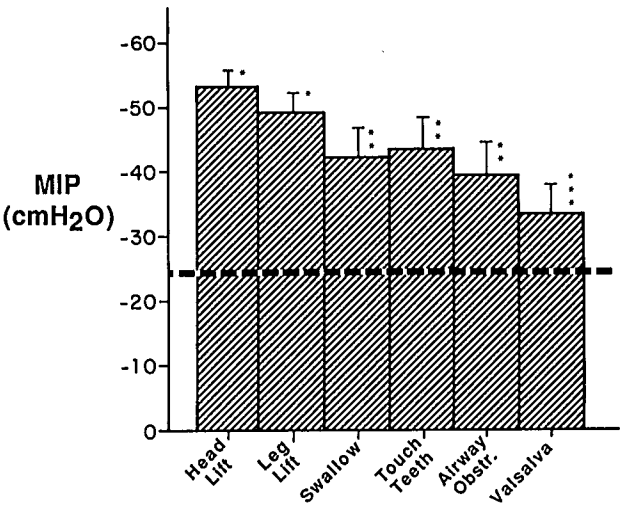

FIG. 2. Levels of neuromuscular blockade with dTc indicated by maximum inspiratory pressure (MIP ± SE) below which indicated clinical maneuvers could not be accomplished. Head lift and straight leg raising are the most sensitive indicators of NM blockade with dTc. No maneuvers indicating airway protection could be accomplished by any of the subjects at MIP of -25 cm H_2O. *$P < .001$ compared with MIP = -25 cm H_2O; **$P < .02$ compared with MIP = -25 cm H_2O; ***$P < .05$ compared with MIP = -25 cm H_2O.

a nondepolarizing muscle relaxant could maintain an adequate spontaneous ventilation "with reserve."[1,4] Use of this value of MIP was further extended to use in patients recovering from ventilatory failure in intensive care units.[2,7]

The diaphragm, which is the most important muscle of inspiration, appears to be the skeletal muscle most resistant to nondepolarizing muscle relaxants. Sparing of the diaphragm, in comparison with other muscle groups, has been established in a number of studies. Wymore and Eisele[8] demonstrated in anesthetized patients that twice the dose of dTc was required to produce reductions in MIP comparable to those observed by thumb twitch. Furthermore, recovery times to 50% and 90% of control thumb twitch were twice as long as those for comparable return of inspiratory muscle function.

Gal and Smith[9] measured had grip strength (HGS), vital capacity, and maximum inspiratory and expiratory pressures in normal unanesthetized volunteers given incremental doses of *D-tc.* At MIP's of 35–40% of control, HGS was 6% of control, while vital capacity had only decreased to 50% of control. Thus, although inspiratory muscle strength was obviously affected to a moderate degree, the flexors of the hand were more severely compromised.[9,10] Our data (fig. 1) are in agreement with those of Gal and Smith.[9] However, we induced a greater degree of paralysis (MIP of −20 cm H_2O in the present study) at which level HGS was unobtainable. However, VC was 40% of control (approximately 2.0 L), while $P_{ET_{CO_2}}$ was normal, demonstrating not only adequate V_E, but preservation of a modest degree of ventilatory reserve (VC approximately, 26 ml/kg: 2.0 liters divided by average subject weight of 76 kg). Of the various clinical tests available for assessing recovery of muscle function, Miller reported that ability to sustain a head lift for 5 s was the most sensitive indicator of residual muscle paresis.[11] The results of the present study are in accord with these findings, and add additional information regarding the ability of this test to predict normal or adequate function of the muscles protecting the airway, was well as muscles of ventilation.

This differential sensitivity of various skeletal muscles led us to investigate the relative sparing of those muscles responsible for maintenance and protection of the upper airway. In a study of unanesthetized volunteers, Gal and Smith[9] referred to a gagging sensation and difficulty in swallowing in most subjects, and airway obstruction requiring chin support in two subjects. In our study, we measured clinical parameters of upper airway protection at different degrees of paralysis compared to MIP, an accepted index of ventilatory adequacy.[1] We also compared the relative sensitivity of sustained head lift and straight leg raising to these clinical tests of airway muscle function. Since these clinical end points were of the "all or none" variety, we related them to the continuum of MIP to compare adequacy of airway protection to the adequacy of ventilation. We thus calculated an MIP_{50} in terms of MIP for each subject; that is, the mean of the minimum MIP at which a maneuver could be accomplished and the maximum MIP at which the subject could not perform the maneuver.

Swallowing is obviously required for clearing oropharyngeal secretions. The MIP_{50} for this protective mechanism was −42 cm H_2O, well above the value of −25 cm H_2O deemed sufficient for maintaining adequate spontaneous ventilation. Thus, those muscles responsible for deglutition are functionally more sensitive to dTc than muscles of inspiration (VC at MIP of −38 cm H_2O was 77% of control). Deglutition or swallowing is comprised of an oral preparatory stage, a pharyngolaryngeal stage, and an esophageal stage.[12] The sequential muscular contractions and their coordination are very complex and beyond the scope of this discussion.

The preparatory phase is thought to involve contraction of the masseters and elevation of the tongue. This is followed by elevation of the glottis toward the hyoid and contraction of the muscles of the oropharynx. Finally, a sequential wave of contraction can be detected in the esophagus. We could easily assess the presence of a swallow by asking the subjects whether the swallow had taken place and confirming this by an esophageal trace. Our study does not allow assessment of which particular skeletal muscles in the sequence of swallowing were most affected. We were impressed with the fact that, although we could observe subjects elevating their glottis toward the hyoid when asked to swallow, the final phase of deglutition did not take place. Thus, the clinical observation of appropriate movement of the thyroid cartilage does not mean "the patient can swallow." Atropine was administered to prevent the formation of oral secretions. In a similar experiment without atropine, one of the subjects could not swallow at a MIP of −40 and, with secretions in the oropharynx, could only describe the sensation as one of "drowning."

A clinical method of assessing the ability of the glottis mechanism to close was not readily apparent. We decided that a Valsalva-like maneuver and the ability of the glottis to withstand a pressure of approximately 30 cm H_2O might give an index of vocal cord approximation. At the greater degree of paralysis when the subjects could not elevate intra-abdominal pressure to this value, manual compression of the subject's abdomen by one of the investigators was utilized. Intra-abdominal pressure was confirmed by the intragastric balloon pressure. The inability to close the glottis became obvious from clinical observation and from measurement of expiratory air flow. Again, glottis closure is not a simple maneuver. Intrinsic muscles of the larynx are involved with the cricoarytenoid

muscles being chiefly responsible. In his review of the mechanism of closure of the human larynx,[13] Fink has pointed out that other aspects of glottis closure may be as important. During a Valsalva maneuver, the glottis is raised to the base of the tongue. In addition, closure of the larynx may involve musculature approximating the false cords. Laryngeal closure may not be effective enough either to take part in a cough or to prevent aspiration of pharyngeal contents at levels of paralysis at which ventilation could be maintained.

Our subjects were understandably most distressed at the point of paralysis at which total airway obstruction occurred. This was not a subtle or an induced end point. The MIP was determined at the point at which complete cessation of airflow took place unless mandibular elevation or "jaw thrust" was carried out by one of the investigators. If the mandible was not supported, obstruction recurred. The MIP_{50} for complete airway obstruction was −39 cm H_2O. One subject experienced a totally obstructed airway at an MIP = −55 cm H_2O. The mechanism of obstruction was that of the tongue obstructing the oropharynx. Both glossal and those muscles responsible for elevating the mandible (masseters) are probably involved in maintenance of an open airway in patient in the supine position. We found that subjects could not elevate their own mandibles (approximate lower and upper incisors) at a MIP_{50} of −43.

In examining the MIP_{50} values for the various maneuvers, wide variation was noted among subjects. In all subjects and for all maneuvers, values of MIP_{50} were greater than −25 cm H_2O.

The mean MIP at which subjects could not sustain a head lift or leg lift for 5 s were −53 and −50 cm H_2O, respectively, confirming the relative sensitivity of these tests to dTc. Of interest was the finding that every subject who could perform a head or leg lift could successfully perform the tests of airway protection and maintenance that we utilized.

This study was conducted with dTc and, therefore, application to other muscle relaxants should be made with caution. We think the general finding that the muscles involved in airway protection are more sensitive to dTc than are those of ventilation is probably true for most, if not all, nondepolarizing muscle relaxants. It is possible that some specific muscle groups are affected quantitatively differently, relative to the diaphragm. Similarly, residual anesthesia may affect the difference between these muscles in two different ways. Inhalational agents are well known to enhance neuromuscular relaxation. This may occur, to varying degrees, with the muscle groups we tested. Furthermore, both airway and ventilatory reflexes may be depressed differently by both narcotics and other anesthetic agents, such that these reflexes may be manifested to different degrees at various drug levels. In the presence of residual anesthesia, the airway compromise secondary to residual muscle relaxant may be increased even more than is the interference with ventilation. As the patient's level of anesthetic agent is diminished, during the recovery period, however, the relative muscle strengths demonstrated in our study can be applied with more confidence.

The clinical implications of this study are concerned with the relative sensitivity of the skeletal musculature involved with maintenance and protection of the airway after nondepolarizing muscle relaxants. It appears that these muscles are functionally inadequate at levels of paralysis at which ventilation and ventilatory reserve are sufficient to allow spontaneous ventilation in the subject with normal lungs. In the patient recovering from paralysis, a greater degree of antagonism of nondepolarizing blockers is required than that which results in a MIP of −25 cm H_2O. These data suggest that, although adequate ventilation may be present, the patient's trachea should either remain intubated until greater muscle strength has returned, or precautions should be taken to prevent both aspiration of oral contents and airway obstruction in the recovery room. The ability to sustain head lift is associated with sufficient strength to protect the airway against both of these complications in otherwise normal patients.

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EDITORIAL VIEWS

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How Should Residual Neuromuscular Blockade be Detected?

RESTORATION OF COMPLETE skeletal muscle strength postoperatively is essential to assure that patients are able to sustain adequate ventilation and cough, and maintain a patent airway. Both laboratory and clinical observations suggest that muscle response to peripheral nerve stimulation (usually the ulnar nerve) adequately measures reversal of nondepolarizing neuromuscular blockade. In fact, peripheral nerve stimulation (*e.g.*, train-of-four) is often utilized in preference to (and in the absence of) tests of ventilation. The logic of this approach is based on the following: first, the diaphragm recovers from the effects of nondepolarizing neuromuscular blocking drugs more rapidly than does the adductor pollicis;[1,2] and, second, at a train-of-four ratio of 0.7, vital capacity returns to normal (~15 to 20 ml/kg) and maximum inspiratory and expiratory force are only slightly depressed (−20 to −25 cm H_2O).[3,4] Thus, these tests, especially a train-of-four ratio > 0.7, have been regarded as effective indicators of clinically satisfactory postoperative neuromuscular recovery. These data and much experience have encouraged some investigators to even assert that a train-of-four ratio of 0.5 reveals clinically adequate antagonism of blockade and recovery of muscular function.[5] Savarese* has even suggested that, "In many patients to whom these drugs have been given in proper dosage and with correct timing, reversal will not be required."

In view of the above, should we be concerned that current criteria for assessing adequacy of neuromuscular function (*i.e.*, a train-of-four ratio of 0.7 or more or a maximum inspiratory pressure of at least −25 cm H_2O) might not be sufficient to predict adequate ventilatory function postoperatively? After all, although patients may come to the postanesthesia care unit (PACU) with subtle degrees of residual neuromuscular blockade,[6] they usually recover complete muscle strength without adverse effect. In addition, even if episodes of respiratory depression or inability to protect the airway did occur, competent recovery room personnel should be able to prevent a permanent adverse effect from occurring. Furthermore, when ventilatory insufficiency occurs in the PACU, a primary cause is often difficult to assign (*i.e.*, is it due to residual neuromuscular blockade, or residual anesthetic, or surgical procedure?). There are, in fact, no outcome data assessing the role of residual paralysis, residual anesthetic, or surgery, or some combination of the three when the occasional case of airway obstruction or inability to dispose of vomitus or oropharyngeal secretions occurs in the recovery room.

However, despite both the lack of outcome data and apparently low frequency of serious problems in the recovery room, several studies suggest that perhaps more rigorous indices of adequacy of neuromuscular function may be required. In 1976, Gal and Smith[7] found that, despite adequate ventilation, pronounced neck and pharyngeal muscle weakness existed when recovering from d-tubocurarine-induced paralysis. In this issue of ANESTHESIOLOGY, Pavlin *et al.*[8] have shown that adequate ventilation in human volunteers recovering from a d-tubocurarine neuromuscular-induced blockade did not necessarily indicate ability to maintain a functionally intact airway. An inspiratory pressure of −25 cm H_2O did not assure muscle strength sufficient for airway protection. Only if volunteers were able to lift their heads for 5 s (associated with inspiratory pressure of greater than −50 cm H_2O) could they perform all maneuvers, including

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* Savarese JJ: Newer muscle relaxants. Thirty-eighth Annual Refresher Course Lectures and Clinical Update Program. American Society of Anesthesiologists, Inc., 1987, p 321

swallowing, which are necessary for protection of the airway.

These findings are clinically important and suggest that classical methods of defining recovery of neuromuscular function may not assure that patients have the ability to maintain a patent airway. There are, however, two caveats that limit unrestricted application of the findings from the study of Pavlin *et al.*[8] On the one hand, they studied an older, now rarely used neuromuscular blocking drug, d-tubocurarine. Differences between the mechanism of action of this and other nondepolarizing neuromuscular blocking drugs may neutralize their findings.[9] On the other hand, their study was conducted in unanesthetized volunteers. Thus, the residual effects of anesthesia and surgery may augment neuromuscular blockade-induced pharyngeal and neck muscle weakness and, therefore, place added importance on the findings of Pavlin *et al.*[8] In my opinion, until contradictory data are produced, the results of Pavlin *et al.*[8] probably should be applied to the use of other nondepolarizing muscle relaxants.

If one accepts the premise that even one case of severe, undetected respiratory depression and hypoxia in the PACU resulting in permanent adverse effect is unacceptable, then our charge as anesthesiologists is to deliver the patient to the PACU in a state unlikely to enhance the chances of respiratory depression and hypoxia. Although well-trained recovery room personnel (*e.g.*, nurses) can treat such a weakness secondary to residual effects of neuromuscular blocking drugs, complete reversal of neuromuscular blockade is the best prevention. The implication of the Pavlin *et al.*[8] study that we should seek more sensitive indices of adequacy of reversal of neuromuscular blockade should be taken seriously.

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