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Accelerometry of Adductor Pollicis Muscle Predicts Recovery of Respiratory Function from Neuromuscular Blockade

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Background: **Residual paralysis increases the risk of pulmonary complications but is difficult to detect. To test the hypothesis that accelerometry predicts effects of residual paralysis on pulmonary and upper airway function, the authors related tests of pulmonary and pharyngeal function to accelerometry of adductor pollicis muscle in 12 partially paralyzed volunteers.**

Methods: **Rocuronium (0.01 mg/kg + 2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered to maintain train-of-four (TOF) ratios (assessed every 15 s) of approximately 0.5 and 0.8 over a period of more than 5 min. The authors evaluated pharyngeal and facial muscle functions during steady state relaxation and performed spirometric measurements every 5 min until recovery. Upper airway obstruction was defined as a mean ratio of expiratory and inspiratory flow at 50% of vital capacity of greater than 1. The TOF ratio associated with "acceptable" pulmonary recovery (forced vital capacity and forced inspiratory volume in 1 s of ≥90% of baseline) was calculated using a linear regression model.**

Results: **At peak blockade (TOF ratio 0.5 ± 0.16), forced inspiratory flow was impaired (53 ± 19%) to a greater degree than forced expiratory flow (75 ± 20%) with a mean ratio of expiratory and inspiratory flow at 50% of vital capacity of 1.18 ± 0.6. Upper airway obstruction, observed in 8 of 12 volunteers, paralleled an impaired ability to swallow reported by 10 of 12 volunteers. In contrast, all volunteers except one could sustain a head lift for more than 5 s. The authors calculated that a mean TOF ratio of 0.56 (95% confidence interval, 0.22–0.71) predicts "acceptable" recovery of forced vital capacity, whereas forced inspiratory volume in 1 s was impaired until a TOF ratio of 0.95 (0.82–1.18) was reached. A 100% recovery of TOF ratio predicts an acceptable recovery of forced vital capacity, forced inspiratory volume in 1 s, and mean ratio of expiratory and inspiratory flow at 50% of vital capacity in 93%, 73%, and 88% of measurements (calculated negative predictive values), respectively.**

Conclusion: **Impaired inspiratory flow and upper airway obstruction frequently occur during minimal neuromuscular blockade (TOF ratio ~0.8), and extubation may put the patient at risk. Although a TOF ratio of unity predicts a high probability of adequate recovery from neuromuscular blockade, respiratory function can still be impaired.**

RESIDUAL neuromuscular blockade is an independent risk factor for postoperative pulmonary complications[1] but is difficult to detect clinically.[2] Although evaluation of the fade of muscular contractions with train-of-four (TOF) stimulation is often used to assess the degree of blockade,[3] neither tactile nor optical assessments by an observer provide the appropriate sensitivity to detect minimal neuromuscular blockade[4] shown to impair variables of pulmonary and pharyngeal function.[5,6]

Accelerometry of thumb adduction providing quantitative data on neuromuscular transmission has been shown to improve detection of residual neuromuscular blockade when compared with tactile evaluation of fade of contractions by an observer.[7] However, because respiratory and adductor pollicis muscles differ in their response to neuromuscular blocking agents,[8] it is unclear whether impaired pulmonary function and upper airway obstruction (UAO), affecting patients' ability to maintain a patent airway and clean secretions, can be predicted from results of accelerometry.

Accordingly, we tested in awake, partially paralyzed, healthy volunteers the hypothesis that accelerometry of thumb adduction predicts effects on respiratory function of residual paralysis.

Materials and Methods

Subjects

After approval by the local ethics committee (Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany) and informed written consent, 12 healthy male volunteers (age, 30.6 ± 3.3 [mean ± SD]) of normal height (184 ± 6 cm) and weight (78 ± 10 kg) were enrolled. Normal pulmonary function was ascertained on a screening visit using a body plethysmograph with integrated spirometer (Masterlab Jaeger, Würzburg, Germany).

During the study, subjects rested in a chair with the upper body raised (30°) and knees flexed (20–30°). The arm was attached to a dorsal splint to immobilize the forearms and fingers, allowing the thumb to move freely.

Measurements

Stimulation electrodes (PNS Electrode; NDM, Dayton, OH) were placed on the cleaned and rubbed skin over the ulnar nerve close to the wrist. The acceleration transducer was applied randomized to the left or right distal phalanx of the thumb, a temperature transducer was fixed to the skin, and the extremity was wrapped with surgical cotton. Accelerometry was performed using a TOF-Watch-Monitor (Organon Teknika, Eppelheim, Germany) as reported previously.[9] Every 15 s in each volunteer, we measured acceleration of a transducer

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taped to the thumb in response to supramaximal TOF ulnar nerve stimulation (2 Hz). We did not use a preload, *i.e.*, the thumb was allowed to move freely.

We assessed respiratory function measuring forced expiratory volume in 1 s and forced inspiratory volume in 1 s (FIV_1) volumes and forced vital capacity (FVC) by spirometry (Jaeger) in an air-conditioned room at constant humidity and temperature (22 ± 1°) at the same time of day. UAO was assessed by calculating the mean ratio of expiratory and inspiratory flow at 50% of vital capacity (MEF_{50}/MIF_{50}) from spirometry and was defined as a ratio of greater than 1.[10,11]

Muscle function tests were performed during steady state neuromuscular blockade at a TOF ratio of approximately 0.5 (peak neuromuscular blockade) and 0.8 (minimal neuromuscular blockade) and after 100% recovery of the TOF ratio. This included testing the ability to drink water with a straw and to indicate whether swallowing was impaired, to seal the mouthpiece of the pneumotachograph during a forced expiratory maneuver while the mouthpiece was checked for close seal, and to sustain a head lift for longer than 5 s. Airway obstruction requiring jaw thrust was noted, if present. For safety, we also continuously monitored heart rate, electrocardiogram, and arterial oxygen saturation (pulse oximetry).

Study Protocol

After determination of the supramaximal stimulation current, we used single-twitch nerve stimulation (0.1 Hz, bipolar pulses of 0.2 ms duration) during a 30-min period of signal stabilization and subsequently switched to TOF mode. After baseline pulmonary function was measured, we injected 0.01 mg/kg rocuronium (Organon Teknika) followed by continuous infusion (2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Over periods of more than 5 min, we maintained TOF ratios of approximately 0.5 and 0.8, respectively, to assess pharyngeal and respiratory functions during steady state relaxation. Furthermore, during recovery from residual neuromuscular blockade, three consecutive spirometric maneuvers were performed every 5 min until the end of the experiment.

Results from each single maneuver were correlated to its corresponding TOF ratio and subsequently were used for statistical analysis. In case of a variability of FVC between the three consecutive respiratory maneuvers of more than 0.2 l, we excluded outliers and performed up to five additional maneuvers until three maneuvers with a variability of 0.2 l or less were achieved.[12] When ability to seal the mouthpiece was impaired, volunteers were assisted. After termination of rocuronium infusion, we continued measurements until all tests were finished and the TOF ratio had recovered to unity for 5 min (endpoint).

Statistics

To relate respiratory function data to the results of accelerometry, we tested the *a priori* null hypothesis that FVC does not correlate with the results of the TOF ratio. A 10% decrease from baseline of FVC and FIV_1 was considered clinically relevant. We calculated the TOF ratio (95% confidence interval) that predicts an "acceptable" recovery of FVC and FIV_1 to 90% of baseline using a linear regression model with patients as random effects (SAS Software, version 6.12; SAS Institute, Cary, NC). To assess the distribution of percentiles of FIV_1 and FVC data, we took 500 bootstrap samples, a modeling method used to determine the accuracy of an estimator, *i.e.*, the 95% confidence regions for the TOF ratio thresholds for mean FIV_1 and FVC responses of 90%.[9,13] The resampling scheme was devised in a two-level fashion to emulate the hierarchical sampling scheme, *i.e.*, a random sample with replacement was drawn from the pool of 12 patients. From each resampled patient, bootstrap samples were drawn from his original spirometric measurements.

We used the McNemar test for comparison of the dichotomous variables of muscle function and the Wilcoxon test to compare to baseline mean values of variables derived from spirometry. Correlation analysis (Pearson) was used to compare the relation between TOF ratios and lung function tests. Data are expressed as mean ± SD. A hypothesis was rejected with an α error P of less than 0.05.

Results

Neuromuscular Function during Steady State Neuromuscular Blockade

Peak Neuromuscular Blockade (TOF Ratio 0.5 ± 0.16). All variables derived from spirometry and also pharyngeal and facial muscle functions were significantly affected by neuromuscular blockade. Forced vital capacity decreased to 78 ± 14% of baseline. Diminution of FIV_1 was more intense when compared with forced expiratory volume in 1 s (53 ± 19 *vs.* 75 ± 20% of baseline). The MEF_{50}/MIF_{50} ratio increased ($P < 0.01$) from 0.87 ± 0.34 at baseline to 1.18 ± 0.6, and relevant UAO (MEF_{50}/MIF_{50} ratio > 1) was observed in two thirds of the volunteers (table 1). Furthermore, the ability to swallow normally was impaired in 10 of 12 volunteers also indicating pharyngeal dysfunction. In contrast, fade of contraction of adductor pollicis muscle was visible in only 1 of 12 volunteers. Despite impaired upper airway function, no jaw thrust was needed, none of the volunteers reported dyspnea, and oxygen saturation remained greater than 96% at all times.

Minimal Residual Neuromuscular Blockade (TOF Ratio 0.83 ± 0.06). Although FVC (94 ± 6% of baseline) had recovered acceptably in 10 of 12 volunteers, FIV_1 (84 ± 11% of baseline) remained impaired in half of volunteers. Even at a TOF ratio of 0.8, the MEF_{50}/MIF_{50}

Table 1. Muscle Function during Recovery from Residual Neuromuscular Blockade in Relation to TOF Ratio (n = 12)

TOF Ratio	Inability to Sustain Head Lift >5 s	Inability to Seal Mouthpiece	Inability to Swallow Normally	"Fade" of Contraction Visible	Upper Airway Obstruction
0.5 ± 0.16	1	11*	10*	1	8*
0.83 ± 0.06	0	5	7*	0	4
1.02 ± 0.01	0	1	1	0	1

Accelerometric and spirometric data are presented as mean ± SD. Upper airway obstruction was defined as a mean ratio of expiratory and inspiratory flow at 50% of vital capacity of greater than 1. Even with the greatest degree of paralysis, fade of thumb adduction was visible only in a single patient, and inability to sustain a head lift was seen in another patient. In contrast, at train-of-four (TOF) ratios of 0.5 and 0.83, upper airway obstruction was observed in 8 and 4 of 12 volunteers, respectively. Swallowing and ability to approximate lips to seal a mouthpiece were impaired in many volunteers until TOF ratio had recovered to unity.

* $P < 0.05$ *vs.* TOF recovery to 1.02 ± 0.01.

ratio was still significantly increased (0.92 ± 0.4, $P < 0.01$) from baseline, and 4 of 12 volunteers showed a ratio of greater than 1. Furthermore, although all volunteers could sustain a head lift for longer than 5 s and fade of thumb contraction was not visible, the ability to swallow normally was still impaired in more than half of the volunteers.

Complete Recovery of TOF Ratio. With recovery of TOF to unity, respiratory function as indicated by FVC, FIV_1, MEF_{50}/MIF_{50} ratio, and the ability to swallow normally had recovered acceptably in 11 of 12 volunteers. However, in a single volunteer, FIV_1 was still markedly impaired (73% of baseline), MEF_{50}/MIF_{50} ratio was high (1.47), and swallowing remained difficult while FVC had already recovered to baseline. Adequate recovery of respiratory function was observed some minutes later.

Prediction of Respiratory Function from TOF Ratio

One hundred sixty-nine comparisons between spirometric and accelerometric measurements were performed in 12 subjects. During residual neuromuscular paralysis, TOF ratios correlated with FVC, forced expiratory volume in 1 s, and FIV_1 and also with MEF_{50}/MIF_{50} ratio ($P < 0.0001$). In a linear regression model, a mean TOF ratio of 0.56 (95% confidence interval, 0.22–0.71) predicted an acceptable (*i.e.*, 90%) recovery of FVC. In contrast, recovery of TOF-ratio to 0.95 (0.82–1.18) is required to predict a 90% recovery of FIV_1 (figs. 1 and 2). A 100% recovery of TOF ratio predicts acceptable recovery of FVC, FIV_1, and MEF_{50}/MEF_{50} ratio in 93%, 73%, and 88% of measurements (calculated negative predictive values), respectively.

Discussion

In healthy volunteers, assessment by accelerometry of the TOF ratio of adductor pollicis muscle is more useful to predict the effects of residual paralysis on respiratory function than visual assessment of fade of thumb adduction or testing the ability to sustain a head lift for longer than 5 s. Even in the absence of anesthetic effects, respiratory and pharyngeal functions can be affected seriously during minimal neuromuscular blockade (TOF ratio ~0.8). In turn, recovery of the TOF ratio to unity indicates a high probability of adequate recovery of respiratory function from neuromuscular blockade.

Methodologic Considerations

To assess pulmonary function, we used FVC and FIV_1, considered highly reproducible.[14] FVC is a sensitive in-

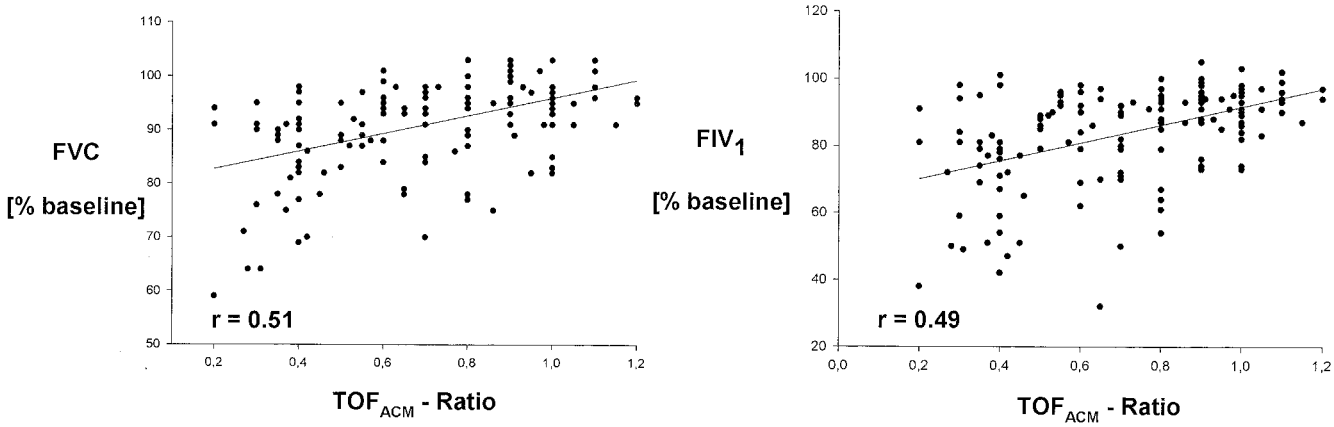

Fig. 1. Forced vital capacity (FVC, *left*, n = 169) and forced inspiratory volume in 1 s (FIV_1, *right*, n = 169) related to TOF ratio during recovery from neuromuscular blockade. TOF ratio correlated significantly ($P < 0.0001$) with FVC and FIV_1. FVC recovered to 90% of baseline or more at a mean TOF_{ACM} ratio of 0.56 (95% confidence interval, 0.22–0.71) whereas FIV_1 was still impaired until a mean TOF_{ACM} ratio of 0.95 (0.82–1.18). With recovery of TOF ratio to unity, FVC and FIV_1 recovered "acceptably" in 93% and 73% of measurements (negative predictive value), respectively.

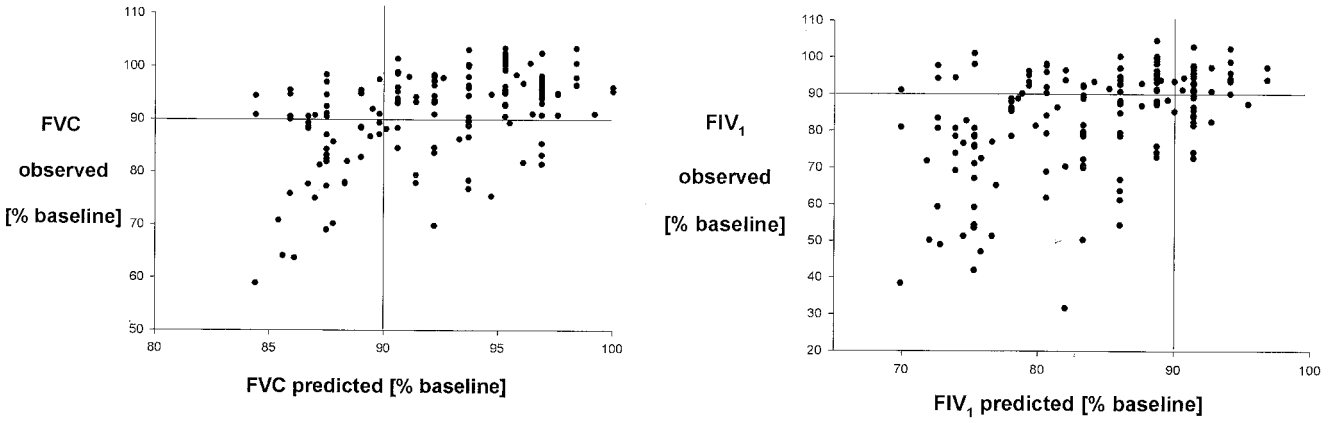

Fig. 2. Relation of predicted and observed determinants of pulmonary function so as to allow optical estimation of predictive values. Forced vital capacity (FVC, *left*) and forced inspiratory volume in 1 s (FIV_1, *right*) as predicted from TOF ratio by linear regression modeling in relation to FVC and FIV_1 measured by spirometry. Lines paralleling the *x* and *y* axes indicate "acceptable" (*i.e.*, 90%) recovery of FVC and FIV_1, respectively.

dicator of development of respiratory symptoms in neuromuscular disease[15,16] and correlates well with respiratory muscle strength.[17] As respiratory muscle weakness can result in an ineffective cough with inability to clear secretions from the airways,[18] we consider FVC recovery relevant for preventing pulmonary complications. To our knowledge, there is no information about the minimum FVC required to avoid an increased risk of pulmonary complications. In patients with amyotrophic lateral sclerosis without symptoms of respiratory weakness, FVC averaged 81% of predicted but 73.5% in those with dyspnea.[15] Although data derived from patients with amyotrophic lateral sclerosis may not be extrapolated to healthy individuals with drug-evoked neuromuscular blockade, we assume that an FVC of 90% should indicate clinically acceptable recovery of pulmonary function.

We did not assess aspiration risk shown to be increased during minimal paralysis.[5] However, we assessed pharyngeal function by testing the patients' ability to swallow and calculated the MEF_{50}/MIF_{50} ratio so as to detect a UAO. Referring to a recent joint statement on respiratory function testing,[19] UAO can be detected from flow-volume loops. The ratio of expiratory and inspiratory flow at 50% of vital capacity obtained by spirometry gradually increases from 0.64 to 1.4 with increasing external resistances[20] and is an established measure of UAO.[10,11,20] In accordance with others,[10,11] we defined an MEF_{50}/MIF_{50} ratio greater than unity as relevant UAO.

Interpretation of Results

An FVC of 78% of baseline observed at peak neuromuscular blockade (TOF ratio 0.5 ± 0.16) is approximately 10% less when compared with values reported previously.[21] Perhaps assessment during maintenance of steady state relaxation rather than during spontaneous recovery from pipecuronium-induced neuromuscular block[21] may have prevented increased neuromuscular function with subsequent consecutive spirometric maneuvers.

Respiratory function can still be markedly impaired when the results of recommended neuromuscular function tests[22,23] suggest adequate neuromuscular recovery. In fact, even at the lowest TOF ratio, fade of muscle contraction was visible in only a single volunteer, whereas upper airway function as well as respiratory function were severely affected in most volunteers. Thus, inadequate neuromuscular recovery with respiratory impairment cannot simply be detected by using a nerve stimulator without measuring quantitatively the muscular response.[4] Furthermore, even in the absence of anesthetic effects, sufficient respiratory recovery cannot be detected reliably when assessing patients' ability to sustain a head lift longer than 5 s.

In contrast, the ability to swallow may be a more sensitive measure of recovery of respiratory function from neuromuscular block, as FIV_1 and FVC were acceptable in almost all measurements and UAO was not observed when the ability of normal swallowing had been recovered. Because the ability to swallow normally can only be assessed after withdrawal of the endotracheal tube, this test may be useful in the recovery room. However, additional clinical variables reliably predicting "safe" extubation would be helpful in practice.

A TOF ratio of 0.56 was calculated to predict acceptable recovery of FVC. This is consistent with the work of Ali *et al.*[24] suggesting that a TOF ratio of 0.6 or more would indicate "adequate respiratory function." However, the authors[24] did not measure inspiratory flow variables. In contrast, our data show that a TOF ratio of 0.6 and even 0.8 is not adequate to ensure recovery of respiratory function as decreased FIV_1, UAO, and impaired ability to swallow were observed until the TOF ratio had recovered to unity. We cannot pinpoint to what degree the effects of neuromuscular blockade on

FIV_1 are evoked by diminution of respiratory muscle strength and/or UAO. However, it is unlikely that the persistent FIV_1 decrease until recovery of the TOF ratio to 0.95 is evoked by residual blockade of respiratory muscles, as inspiratory muscles are less affected by curarization than expiratory muscles.[25] Rather, decreased inspiratory flow may be evoked by UAO.[10,20] In accordance, our data demonstrate, in parallel to an FIV_1 decrease, a persistent increase of MEF_{50}/MIF_{50} ratio even at minimal neuromuscular blockade.

The response to relaxants of respiratory and adductor pollicis muscles varied between individuals. This variability was most intense in one volunteer differing markedly from the other volunteers in the response to rocuronium of adductor pollicis contraction and respiratory function. Although TOF ratio and FVC had recovered to baseline, FIV_1 and MEF_{50}/MIF_{50} ratio were still markedly impaired (73% and 1.47, respectively), and swallowing remained difficult for some minutes. Therefore, although a TOF ratio of 1 predicts recovery of FVC, pharyngeal and respiratory functions may be still impaired in some patients.

Residual neuromuscular block increases the risk of postoperative pulmonary complications,[1] possibly by an attenuated ventilatory response to hypoxemia[26] or because of increased incidence of aspiration resulting from functional impairment of pharyngeal and upper esophageal muscles.[5] Because respiratory and pharyngeal functions can be affected seriously even during minimal neuromuscular blockade (TOF ratio of 0.8), premature extubation may put the patient at an increased risk of respiratory complications. This suggestion is supported by a recent report[5] demonstrating by pharyngeal videoradiography an increase in the incidence of pharyngeal dysfunction even after recovery of the TOF ratio to 0.9 or more.[5]

When the TOF ratio has recovered to unity, FVC, FIV_1, and MEF_{50}/MIF_{50} ratio have recovered in 93, 73, and 88% of measurements (negative predictive values), respectively. Thus, a TOF ratio of 1 may be a useful criterion so as to minimize the risk of relevant residual neuromuscular blockade on respiratory function. Of note, however, the clinician also has to consider that accelerometry cannot exclude the impact of other variables known to affect postoperative respiratory function such as underlying disease, anesthetics, analgesics, and surgery.

In summary, optical assessment of the fade of thumb adduction after ulnar nerve stimulation or testing the ability to sustain a head lift for longer than 5 s are inappropriate to detect effects of residual neuromuscular blockade on respiratory function. Even in the absence of anesthetic effects, impaired inspiratory flow and UAO frequently occur during minimal neuromuscular blockade (TOF ratio ~0.8), and extubation may put the patient at risk. Although a TOF ratio of unity predicts a high probability of adequate recovery from neuromuscular blockade, respiratory function can still be impaired.

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