Fade of Pulmonary Function During Residual Neuromuscular Blockade*

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Objectives: **A decrement in evoked muscle force with repetitive nerve stimulation (fade) suggests impaired neuromuscular transmission. We tested the hypothesis that fade of pulmonary function, *ie*, a decrease in values of FVC with the second spirometric maneuver compared to the first maneuver, occurs during impaired neuromuscular transmission.**
Design: **Prospective study.**
Participants: **Six healthy male volunteers.**
Interventions: **A series of three consecutive spirometric maneuvers was performed every 5 min in six awake healthy volunteers before, during, and after partial paralysis evoked by rocuronium (0.01 mg/kg IV plus 2 to 8 μg/kg/min).**
Measurements and results: **We measured FVC, FEV_1, forced inspiratory volume in 1 s (FIV_1), peak expiratory flow (PEF), and peak inspiratory flow (PIF) by spirometry, and force of adductor pollicis muscle by mechanomyography (train-of-four [TOF] stimulation). A statistically significant fade (reduction of the second maneuver from the first maneuver) of FVC, FEV_1, FIV_1, PEF, and PIF was observed during neuromuscular blockade. With peak relaxation (TOF ratio, 0.5) fade amounted to medians of 10% (interquartile range [IQR], 9 to 23%), 7% (IQR, 2 to 16%), 31 (IQR, 19 to 47%), 9% (IQR, 3 to 24%), and 30% (IQR, 5 to 43%), respectively. A fade of ≥ 10% was always associated with a clinically relevant (≥ 10%) FVC reduction from baseline (*ie*, FVC before rocuronium administration). However, FVC reduction from baseline was still present in 23% of measurements without a relevant FVC fade.**
Conclusions: **A clinically relevant fall (fade) in FVC from the first to the second value during or after neuromuscular blockade suggests impaired pulmonary function and may be due to muscle paralysis. For this reason, the first (best) FVC value may overestimate pulmonary function and expose the patient to an unidentified risk.** ***(CHEST 2005; 127:1703–1709)***

Key words: myasthenia gravis; partial paralysis; spirometry; weaning

Abbreviations: FIV_1 = forced inspiratory volume in 1 s; IQR = interquartile range; NBA = neuromuscular blocking agent; PEF = peak expiratory flow; PIF = peak inspiratory flow; TOF = train-of-four

Neuromuscular blocking agents (NBAs) are used to achieve surgical relaxation, facilitate mechanical ventilation, or assist in the treatment of increased intracranial pressure in critically ill patients.[1] However, residual neuromuscular blockade evoking muscle weakness lasting for up to 1 week occurs frequently after prolonged administration of NBAs.[2] Furthermore, residual neuromuscular blockade is an independent risk factor for postoperative pulmonary complications[3] but is difficult to detect clinically.[4]

Residual neuromuscular blockade can be determined by assessing fade of successive muscle contractions during repetitive nerve stimulation. In particular, evaluation of the fade of adductor pollicis contractions with a train-of-four (TOF) ulnar nerve stimulation is commonly used to assess residual neuromuscular blockade.[5] However, this technique has some limitations in practice. First, the response of adductor pollicis and respiratory muscles to NBAs can vary.[6,7] After bolus administration of vecuronium, patients can acquire paralysis of the respiratory muscles but not of the adductor pollicis.[6] Furthermore, there can be differences in response by

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various respiratory muscles to NBAs. Pharyngeal muscles are suggested to be most susceptible to NBAs followed by intercostal muscles, while the diaphragm seems to be least susceptible.[8] Second, in critically ill patients, neuromuscular monitoring of adductor pollicis may be difficult, because peripheral edema increases the resistance between the stimulus electrodes and the ulnar nerve.[1] In contrast, spirometric measurements, often quoted as predictors of weaning from mechanical ventilation,[9,10] may be useful to detect the effects of NBAs on respiratory function. Therefore, we tested the hypothesis that a clinically relevant fade, *ie*, a 10% decrease of FVC, occurs with two consecutive maneuvers during residual neuromuscular blockade.

Materials and Methods

Subjects

After approval by the local ethics committee and written informed consent, six healthy male volunteers (mean age, 29.3 ± 2.6 years [± SD]) of normal height (mean, 183 ± 5 cm) and weight (mean, 79 ± 10 kg) were enrolled. Excluded were volunteers with a history of neuromuscular, cardiovascular, pulmonary, renal, hepatic, or neurologic disorders. Baseline pulmonary functions were measured on screening visits using a body plethysmograph with an integrated spirometer (Masterlab; Jaeger; Würzburg, Germany).

Measurements

Since subject cooperation is essential to achieve valid spirometric measurements,[11] we trained the volunteers in performing spirometric tests both during the first screening visit and the day of the main study. Furthermore, they were coached throughout each maneuver by word and body language so as to maximize their effort. Volunteers rested in a chair with the upper body raised (30°) and knees flexed (20 to 30°). FVC, FEV_1, forced inspiratory volume in 1 s (FIV_1), peak expiratory flow (PEF), and peak inspiratory flow (PIF) were measured in a series of three using pneumotachography (Jaeger) in an air-conditioned room at constant humidity and temperature (22 ± 1°) at the same time of the day.

We measured by mechanomyography evoked force of the adductor pollicis muscle in response to supramaximal ulnar nerve stimulation using a Grass force transducer (LB 8000; Maywood Instruments; Basingstoke, UK) and a dedicated measurement system (Model Relaxometer 2; University of Groningen; Groningen, the Netherlands).[12] During a 30-min period of signal stabilization, we applied single twitch nerve stimuli (0.1 Hz, bipolar pulses of 0.2 ms in duration) and subsequently switched to train-of-four (TOF) stimulation (2 Hz) every 15 s. For safety, we also continuously monitored heart rate (ECG) and arterial oxygen saturation (pulse oximetry).

Study Protocol

After determination of supramaximal ulnar nerve stimulation current and signal stabilization, baseline pulmonary function was measured. Three spirometric maneuvers were performed allowing three tidal volumes to elapse between the consecutive maneuvers. The timing interval used to identify fade, *ie*, from the beginning of the first to the beginning of the second spirometric maneuver, averaged 41 ± 15 s (range, 30 to 75 s). If a volunteer indicated that a maneuver was not sufficiently performed, or an investigator detected a volunteer's inability to seal the mouthpiece, the complete series (up to three measurements) were excluded. The series was repeated 5 min later, and the volunteer, if not able to seal the mouthpiece, was assisted by an investigator. We ensured by optical assessment of the flow-volume loops that this approach was sufficient to detect outliers.

After baseline spirometric measurements were performed (a series of three), rocuronium (0.01 mg/kg; Organon Teknika; Eppelheim, Germany) was injected followed by continuous infusion (2 to 8 μg/kg/min). Over a period of approximately 5 min, two separate steady-state levels were achieved at TOF ratios of 0.5 (peak neuromuscular blockade) and 0.8 (minimal neuromuscular blockade).

We performed a series of three spirometric maneuvers at steady-state relaxation, and also during recovery from residual neuromuscular blockade every 5 min. After termination of the rocuronium infusion, we continued the measurements until all tests were finished and the TOF ratios had completely recovered (end point).

Data Analysis

Data are expressed as median (interquartile range [IQR]). A power analysis from data reported previously[7] revealed that a sample size of six volunteers would be sufficient to detect a significant fade (power = 0.8, $p = 0.05$). In particular, we took into account a correlation coefficient of 0.92 between the two consecutive measurements of FVC, a difference to be detected of 0.5 L, and a between patient variation (σ^2) of the differences between the first and the second FVC maneuvers of 0.14 L. The *a priori* null hypothesis was that FVC does not decrease significantly at peak neuromuscular blockade with the second maneuver compared to the first spirometric maneuver. We used a paired-sample test for comparison of the first and second maneuvers rather than repeated-measures analysis of variance, as FVC decreased significantly with the second spirometric maneuver but did not decrease further with the third maneuver.

TOF ratio and FVC fade were compared by two-tailed correlation analysis (Pearson). We applied a Bland-Altman analysis[13] to evaluate the mean differences (bias) and the twofold SDs (upper and lower limits of agreement) between both methods of neuromuscular transmission monitoring. The Wilcoxon test and McNemar test were also used, as appropriate. Software (V 10.0; SPSS; Chicago, IL) was used for statistical analysis. An α level of 0.05 was used for statistical significance.

Results

A total of 165 spirometric maneuvers were performed in six volunteers. During neuromuscular blockade (n = 129 measurements), FVC, FEV_1, FIV_1, PEF, and PIF decreased significantly with the second spirometric maneuver but did not decrease further with the third maneuver.

Fade of Pulmonary Function

At peak neuromuscular blockade (TOF ratio, 0.5), there were significant reductions between the sec-