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, i.e., 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, FEV₁, forced inspiratory volume in 1 s (FIV₁), 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, FEV₁, FIV₁, 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 (i.e., 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.

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

Abbreviations: FIV₁ = 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. However, residual neuromuscular blockade evoking muscle weakness lasting for up to 1 week occurs frequently after prolonged administration of NBAs. Furthermore, residual neuromuscular blockade is an independent risk factor for postoperative pulmonary complications but is difficult to detect clinically.

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. However, this technique has some limitations in practice. First, the response of adductor pollicis and respiratory muscles to NBAs can vary. After bolus administration of vecuronium, patients can acquire paralysis of the respiratory muscles but not of the adductor pollicis. Furthermore, there can be differences in response by...
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. 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. In contrast, spirometric measurements, often quoted as predictors of clinically relevant fade, 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]; mean height, 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 and an integrated spirometer (Masterlab; Jaeger; Würzburg, Germany).

**Measurements**

Since subject cooperation is essential to achieve valid spirometric measurements, 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, FEV1, forced expiratory flow in 1 s (FEV1), forced inspiratory volume in 1 s (FIV1), peak expiratory flow (PEF), and peak inspiratory flow (PIF) were measured in a series of three 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 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 (σ2) 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 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, FEV1, FIV1, 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-
ond and first spirometric maneuvers of FVC (means, 4.37 ± 0.87% vs 3.8 ± 0.76%), FEV₁ (mean, 3.64 ± 0.78% vs 3.25 ± 0.65%), FIV₁ (mean, 3.85 ± 0.75% vs 2.73 ± 1.06%), PEF (mean, 7.21 ± 1.3% vs 6.09 ± 1.3%), and PIF (mean, 4.68 ± 1.1% vs 3.43 ± 1.0%), respectively. The medians and IQRs of these differences between the second and first spirometric maneuvers amounted to 10% (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. The difference of FVC, FEV₂, FIV₁ were marked (Δ₂₃ > 0.2 L) in five of six volunteers among all the variables. In contrast, pulmonary function did not decrease further between the second and third maneuvers within a series (Fig 1). Even at minimal neuromuscular blockade (TOF ratio, 0.8), fade of pulmonary function was observed for FVC, FIV₁ (Fig 2), PEF, and PIF. A clinically relevant (≥ 10%) fade was associated with a 10% FVC reduction from baseline with all the measurements, while the FVC reduction was still present in 23% of measurements without a relevant FVC fade. Fade of pulmonary function disappeared with recovery from neuromuscular blockade (TOF ratio, 1.0), as shown in Figure 2.

Agreement of TOF Fade and FVC Fade

During neuromuscular blockade, TOF fade was significantly greater than FVC fade, with a mean difference (bias) of ratios of 0.25 (SD, 0.16; p < 0.0001). Bland and Altman analysis also revealed that limits of agreement were wide, as depicted in Figure 3. Correlation between TOF fade and FVC fade was poor (r = 0.21).

Impairment of Pulmonary Function During Neuromuscular Blockade

Neuromuscular blockade per se significantly lowered all of the spirometric variables. At peak blockade (TOF ratio, 0.5) FVC decreased to 80% (IQR, 81 to 96%) of baseline, indicating impaired respiratory muscle strength. Peak effects of neuromuscular blockade on FIV₁ and PIF were 70% (IQR, 52 to 85%) and 64% (IQR, 47 to 86%) of baseline, respectively and were significantly greater than those on expiratory flow variables (FEV₂ and PEF: 87% [IQR, 84 to 91] and 80% [IQR, 73 to 93%]), respectively. Despite impaired pulmonary function oxygen saturation remained > 96% at all times.

Discussion

During impaired neuromuscular transmission, fade of pulmonary function was observed with standard pulmonary function tests so that FVC, FEV₁, FIV₁, PEF, and PIF decreased significantly with the second maneuver.

Critique of Methods

In cases of large variability in FVC, the ATS committee on standards of pulmonary function testing recommends performing up to eight maneuvers and to exclude outliers so as to achieve three acceptable forced respiratory curves. However, this approach would have excluded a test of the hypothesis raised since a fade of pulmonary function cannot be discriminated from an "outlier." Therefore, we used a different approach to achieve acceptable spirometric measurements: If a volunteer, appropriately trained in performing spirometric measurements, indicated that he did not perform the maneuver adequately, or a volunteer’s inability to seal the mouthpiece was detected, the particular series of measurements was excluded and repeated 5 min later while the volunteer was assisted with sealing the mouthpiece, if required.

We choose FVC as the main criteria as it is a sensitive indicator of development of respiratory weakness in neuromuscular disease and correlates well with respiratory muscle strength. In contrast, to our knowledge the clinical relevance of a slight inspiratory flow limitation (e.g., FIV₁ reduction) is unknown, especially since intubated patients who are being tested for extubation readiness would not be subject to upper airway obstruction from residual paralysis. We measured neuromuscular function by mechanomyography, which provided the “gold standard” of neuromuscular transmission monitoring.

We intended to limit the number of patients to be included, as supramaximal nerve stimulation in volunteers during neuromuscular blockade may be associated with serious complications, and the procedure is also associated with discomfort for the volunteers. The number of six volunteers included may be considered small. However, this decision is based on a sample size estimation from previously reported data. We calculated that a sample size of six volunteers would be adequate to find a ≥ 10% reduction of FVC from the first to the second spirometric maneuvers. Given the excellent reproducibility of FVC measurements, we considered a 10% difference clinically relevant, minimizing the bias on the hypothesis studied of regression to the mean, i.e., the tendency that a random variable will ultimately have a value closer to its mean value, and of normal variability. Thus, the methods used were appropriate to test the hypothesis raised.

Interpretation of Results

The ATS statement on standardization of spirometry recommends that when interpreting FVC, FEV₁, and PEF, the highest spirometric reading of a testing series should be used. This recommenda-
Figure 1. Values of variables derived from the first and second spirometric maneuvers within a series of three maneuvers at peak neuromuscular blockade. With the second maneuver, FVC and FEV₁ decreased in all volunteers. FIV₁, PIF, and PEF decreased in all but one volunteer, and fade of pulmonary function was significant with all variables. Medians and IQRs are given from the first and third spirometric measurements.
tion is based on the assumption that the highest result best reflects a patient’s pulmonary function. Furthermore, the recommendation implies that the particular order of a maneuver within a series does not substantially influence its results. Our data show, however, that this assumption is not appropriate during impaired neuromuscular transmission. Even with minimal neuromuscular blockade, values obtained from the second spirometric maneuver were significantly lower compared to the first maneuver. Furthermore, at peak neuromuscular blockade, fade of FVC was > 0.2 L in all but one volunteer, and thus the “variability” between consecutive spirometric maneuvers also exceeded the maximum variability recommended of 0.2 L for spirometric measurements. Accordingly, when residual neuromuscular blockade is present, it is not useful to consider for analysis only the largest of three spirometric maneuvers, as this does not take into account patients’ FVC fade from neuromuscular transmission failure.

Figure 2. Medians and IQRs of spirometric fade, i.e., differences between the second and the first spirometric maneuvers (percentage of first spirometric measurement within a series). Values are given before relaxation (baseline), at peak neuromuscular blockade (TOF ratio, 0.5), at minimal neuromuscular blockade (TOF ratio, 0.8), and after recovery (TOF ratio, ≥ 1). At peak relaxation, differences between the second and the first spirometric maneuvers were significant with FVC, FIV1, and FEV1. During minimal neuromuscular blockade (TOF ratio, 0.8), FVC and FIV1 were still decreased. *p < 0.05 vs baseline.

Figure 3. Bland-Altman-plot of the difference against the mean of the evoked TOF fade and FVC fade (ratio of the second and first spirometric maneuvers). Data are derived from 86 spirometric measurements in six volunteers. Lines indicate mean difference (bias) and upper and twofold SD (upper and lower limits of agreement). Values of TOF fade were significantly (p < 0.0001) greater than values of FVC fade, with a mean difference (bias) of 0.25 ± 0.16.
Furthermore, FVC fade may indicate effects of residual neuromuscular blockade on respiratory function. This information may be of interest, as quantitative TOF monitoring is not routinely used in practice,

and baseline spirometric data may not be available. In our study, during neuromuscular blockade a clinically relevant FVC fade of ≥ 10% was always associated with a relevant (ie, 10%) FVC reduction from baseline. In contrast, a relevant FVC fade did not occur at baseline nor after 100% recovery of TOF ratio. Thus, a relevant fade observed after administration of neuromuscular blocking agents is unlikely to be a random effect but rather the result of residual paralysis. However, absence of FVC fade does not exclude the potential effects of relaxation on respiratory function as a FVC reduction was also observed without relevant FVC fade. Therefore, when residual effects of neuromuscular blockade on respiratory function are assumed from FVC fade, assessment should be accompanied by quantitative monitoring of TOF ratio. The combination of FVC fade and TOF fade will confirm that reversal of neuromuscular blockade is required.

Our findings were obtained in volunteers trained in performing spirometric measurements, and recovery of neuromuscular blockade was the only abnormality present. Any conclusions drawn in this idealized setting, therefore, cannot be directly applied to patients receiving mechanical ventilation. Reproducibility of spirometric measurements may differ between volunteers and patients, and the influence on FVC fade in the presence of other variables known to affect respiratory function such as underlying disease, anesthetics, analgesics, and surgery remain unknown. Similar studies in patients recovering from a period of mechanical ventilation and neuromuscular blockade are required to determine whether FVC fade will be a useful additional test to detect respiratory effects of residual neuromuscular blockade in a susceptible patient population.

Tetanic fade, ie, a decrease in force of a muscle with evoked repetitive muscle contractions, was the most likely mechanism of the decreased pulmonary function during partial neuromuscular blockade. This is probably related to the decay in presynaptic acetylcholine output per stimulus with repetitive contractions, and given the interaction of postsynaptic acetylcholine receptors with NBAs, excitation of some muscle fibers becomes subthreshold. However, posttetanic potentiation, ie, an increase of force after sustained muscle contractions, may also play a role during repetitive forced spirometric maneuvers. The degree of posttetanic potentiation is likely to be influenced by the amount of effort and number of repetitions of the spirometric maneuvers. To avoid any possible increase in variability of FVC fade, the time between spirometric maneuvers should be standardized (we choose three tidal volumes to elapse between two consecutive spirometric maneuvers).

In our study, inspiratory flow rates were depressed more than expiratory flow rates and FVC. It is unlikely that the marked effects on FIV₁ and PIF are due to residual blockade of respiratory muscles, as inspiratory muscles are less affected by neuromuscular blockade than expiratory muscles. Rather, persistent inspiratory flow limitation may be evoked by upper airway obstruction. Even when the neuromuscular transmission is only slightly impaired (TOF ratio, 0.5 to 0.8), a significant FVC decrease may occur, suggesting impaired respiratory muscle strength. As respiratory muscle weakness can result in an ineffective cough with inability to clear secretions from the airways, we consider FVC recovery crucial for preventing pulmonary complications. As FVC fade predicts effects of relaxation on respiratory muscles, FVC fade may be a viable monitoring method to detect respiratory effects of residual neuromuscular blockade.

CONCLUSION

During partial neuromuscular blockade, a fade in pulmonary function occurs as measured by spirometry. The clinician should consider that a clinically relevant (≥ 10%) fade of pulmonary function suggests possible residual neuromuscular blockade. Further studies in patients recovering from a period of mechanical ventilation and neuromuscular blockade are needed to evaluate whether FVC fade is a useful method for enhanced monitoring of recovery from neuromuscular blockade in a susceptible patient population. If recovery of pulmonary function is assessed, focusing only on the first (best) measurement of three, might significantly overestimate pulmonary function and expose the patient to an unidentified risk.

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